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Practical synthesis and electronic study of non-spiro and spiropyrano[2,3-c]pyrazole-3-carboxylate derivatives via uncatalyzed domino one-pot, four-component reactions

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Abstract: A practical and efficient synthesis of non-spiro and spiropyrano[2,3-c]pyrazole-3-carboxylate derivatives was developed. The synthesis was achieved via a domino one-pot, four-component reaction of diethyl oxaloacetate, hydrazine, aldehyde and malanonitrile in refluxing acidic ethanolic solution under non-catalytic system. This method is rapid, simple and provides products in good yields and can be accessed via different classes of carbonyls, malanonitriles and hydrazine derivatives. Mechanistic study envisaged that this domino four-component reaction proceeds via sequential reactions of pyrazolone formation, Michael reaction and Thorpe-Ziegler cyclization reaction. Strong electronic effects of Knoevenagel and pyrozolone product contribute significantly towards successful cyclization of the title compounds.

Keywords: Pyrano[2,3-c]pyrazole-3-carboxylate; diethyloxaloacetate; Michael reaction.

1. Introduction

Highly functionalized pyrano[*2,3-c*]pyrazoles represent an important class of biologically active heterocyclic compounds. They were reported as antimicrobial,[1] analgesic,[2] vasodilator,[3] anticancer,[4,5] anti-inflammatory agents,[6] inhibitors of human Chkl kinase,[7] antifungicidal agents,[9] and also as biodegradable agrochemicals[10] (Figure 1). Potential biological activities and widespread synthetic utilities have led to the identification of them as an important class of heterocyclic compounds, which has created considerable interests in pharmaceutical industries and in diversified fields of organic synthesis.[11] Practically, the construction of pyrano[2,3-*c*]pyrazole has been elegantly established through different modes of reactions and cyclization of two-, three- and four-component reactions.

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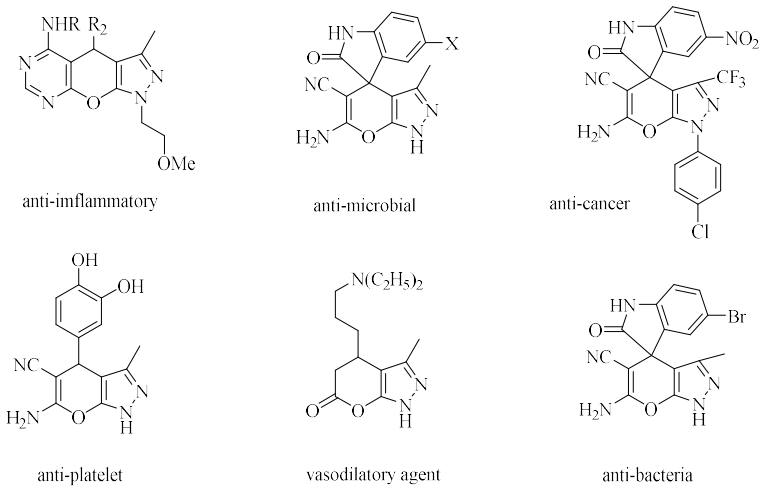


Figure1. Biologically active pyranopyrazole compounds

Previously pyrano[2,3-*c*]pyrazole was synthesized by a reaction between 3-methyl-1-phenylpyrazoline-5-one and tetracyanoethylene in a two-component type reaction.[12] Subsequently, Otto and co-workers successfully demonstrated a base catalyzed two-component Michael type reaction between 4-arylidiene-1-phenyl-1*H*-pyrazole-5-one and malononitrile for the synthesis of 4-aryl-pyrano[2,3-*c*]pyrazole derivatives.[13] In addition, several groups have shown that weak bases can also be used for this Michael type of cyclization. On the other hand, Shestopalov and co-workers had reported the use of base catalyzed three-component reaction of pyrazol-5-one, aldehydes and malononitriles in their synthesis of spiro-pyrazolopyrans.[14]

In a different development, Zhang et al. had successfully reported on an efficient synthesis of different pyranopyrazole derivatives, using ethyl acetoacetate as the β-keto ester through meglumine promoted four-component reaction.[11] Zonouz et al. also reported on an efficient four-component reaction of dimethyl acetylenedicarboxylate, hydrazine hydrate, malononitrile, and aromatic aldehydes for the synthesis of 2,4-dihydropyrano[2,3-*c*]pyrazoles-3-carboxylate in water.[15] To date the most common reagents involved in four-component reactions pertaining to pyranopyrazole synthesis are hydrazines, β-ketoester, aldehydes and malanonitriles.

Interestingly, with regards to our literature searches there is only a single report that employed diethyl oxaloacetate as the source of the active methylene group despite diverse synthetic approaches reported on the construction of derivative of pyranopyrazole. This one-pot reaction was successfully demonstrated by Gein et al. in the synthesis of ethyl 6-amino-4-aryl-5cyano-1,4-dihydropyrano[*2,3-c*]pyrazole-3-carboxylates using four-component two-parallel reaction manner.[16] It was reported before that diethyl oxaloacetate is a non-common source of active methylene group in most of the one-pot reactions as it bears two active ester groups which highly likely to undergo multiple substitution reactions as compared to similar alkyl acetoacetate.[17]

As in continuation of our endeavor on the synthesis of biologically active heterocyclic organic compounds, herein we report a simple synthesis of pyranopyrazoles by a domino four component reaction of aldehydes, diethyl oxaloacetate, malononitrile and hydrazine.[18,19,20,21] This method was practical and environmentally friendly as it was carried out in cheap solvent (ethanol) without any catalysts or chromatographic purification processes and gave high product yields within 30 minutes.

2. Experimental

Melting points were determined on an automatic FP62 melting point apparatus from Mettler Toledo and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JOEL NMR Spectrometer instrument operating at 400 MHz at room temperature, in $CDCl_3$ or DMSO solutions. Chemical shift values are given in δ units (ppm) relative to TMS as internal standard. Elemental analyses were performed on the Flash Elemental Analyzer 110 series. IR spectra (4000-400 cm^{-1}) were recorded on Varian Excalibur 3100 FT-IR

spectrometer, using ATR. The progress of the reactions was routinely monitored by thin layer chromatography (TLC) on silica gel GF254 and the products were visualized with an ultraviolet lamp (254 and 365 nm). All reagents and starting materials were purchased from Sigma-Aldrich Co. and Merck Chemical Co.

2.1. Chemistry

*2.1.1 General procedure for the synthesis of pyrano-pyrazole **1a-1t**.*

To a solution of diethyloxalacetate sodium salt (5.5 mmol) in 20 ml ethanol was added 35% hydrazine solution (5.5 mmol) and 1 ml of acetic acid and refluxed for 15 minutes. Carbonyl compound (5 mmol) and malononitrile (5 mmol) were then added to the reaction mixture, and heating was continued for additional 15 minutes. The reaction mixture was left to cool and the resulting solid was filtered off and washed with water to furnish the pure product.

*2.1.2 Synthesis of ethyl 6-amino-5-cyano-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate(**1a**),* Following the above mentioned procedure, **1a** was isolated as a white solid (82%). m.p 226-227 °C. IR *v* cm^{-1}: 3388 (NH_2), 3218 (NH), 2199 (CN), 1716 (COOEt), 1651 (C=C). δ_H (DMSO, 400 MHz): 7.28-7.22 (m, 2H, Ar H), 7.19-7.13 (m, 1H, Ar H), 7.08-7.03 (m, 2H, Ar H), 6.99 (s, 2H, NH_2), 4.71 (s, 1H, CH), 4.04 (q, J = 7.2 Hz, 2H, CH_2), 1.00 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.5 (CNH_2), 158.6 (C=O), 156.1 (CNH), 145.4 (quat. Ar C), 129.5 (C=N), 128.7 (Ar C), 127.8 (Ar C), 127.1 (Ar C), 120.8 (CN), 104.1 (quat. C), 61.3 (CH_2), 58.3 (quat. C), 37.5 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{14}N_4O_3$, C 61.93, H 4.55, N 18.06. Found: C 62.04, H 4.52, N 20.83.

*2.1.3 Synthesis of ethyl 6-amino-5-cyano-4-(4-methoxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1b**),* Following the above mentioned procedure, **1b** was isolated as a white solid (65%), m.p 235-236 °C; IR spectrum, *v*, cm^{-1}: 3429 (NH_2), 33180 (NH), 2195 (CN), 1717 (COOEt), 1633 (C=C); δ_H (400 MHz, DMSO): 7.02-6.97 (m, 2H, Ar H), 6.95 (s, 2H, NH_2), 6.81-6.77 (m, 2H, Ar H), 4.65 (s, 1H, CH), 4.08-4.03 (q, J = 7.0, 2H, CH_2), 3.66 (s, 3H, CH_3), 1.06-1.03 (t, J = 7.1, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO): 160.4 (CNH_2), 158.7 (C=O), 158.4 (CNH), 137.6 (Ar C), 130.5 (Ar C), 128.8 (Ar C), 127.1 (Ar C), 120.9 (CN), 114.9 (quat. C), 114.1 (quat. C), 104.5 (quat. C), 61.3 (CH_2), 58.6 (quat. C), 55.5 (OCH_3), 36.7 (CH), 14.3 (CH_3); Anal. calc. for $C_{17}H_{16}N_4O_4$, C 59.99, H 4.74, N 16.46. Found: C 54.59, H 3.51, N 22.27.

*2.1.4 Synthesis of ethyl 6-amino-5-cyano-4-(4-ethoxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1c**)*, Following the above mentioned procedure, **1c** was isolated as a yellowish solid (60%), m.p 210-211 °C. IR *v* cm^{-1}: 3413 (NH_2), 3290 (NH), 2206 (CN), 1740 (COOEt), 1660 (C=C). δ_H (DMSO, 400 MHz): 6.97-6.92 (m, 4H, NH_2 Ar H), 6.80-6.75 (m, 2H, Ar H), 4.64 (s, 1H, CH), 4.06 (q, J = 7.2 Hz, 2H, CH_2), 3.92 (q, J = 7.0 Hz, 2H, CH_2), 1.25 (t, J = 6.9 Hz, 3H, CH_3), 1.05 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.4 (CNH_2), 158.7 (C=O), 157.6 (quat C), 137.4 (quat. Ar C), 129.4 (quat C), 128.8 (Ar C), 120.9 (CN), 114.5 (Ar C), 104.5 (quat. C), 63.4 (CH_2), 61.3 (CH_2), 58.6 (quat. C), 36.71 (CH), 15.19 (CH_3), 14.3 (CH_3); Anal. calc. for $C_{18}H_{18}N_4O_4$, C 61.01, H 5.12, N 15.81. Found: C 59.53, H 4.93, N 17.36.

*2.1.5 Synthesis of ethyl 6-amino-5-cyano-4-(4-ethylphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1d**)*. Following the above mentioned procedure, **1d** was isolated as a yellowish solid 69%, mp 212-213 °C; IR spectrum, *v*, cm^{-1}: 3433 (NH_2), 3155 (NH), 2194 (CN), 1727 (COOEt), 1631 (C=C). δ_H (DMSO. 400 MHz,): 7.07 (m, 3H, Ar H), 6.96 (m, 1H, Ar H), 6.94 (s, 2H, NH_2), 4.67 (s, 1H, CH), 4.05 (q, J = 7.1, 2H, CH_2), 2.52 (q, J = 7.5 Hz, 2H, CH_2), 1.10 (t, J = 7.5 Hz, 3H, CH_3), 1.01 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (DMSO, 100 MHz): 160.5 (CNH_2), 158.7 (C=O), 156.1 (CNH), 142.8 (quat. Ar C), 142.5 (quat. Ar C), 129.4 (quat C), 128.1 (Ar C), 127.7 (Ar C), 120.9 (CN), 104.3 (quat. C), 61.3 (CH_2), 58.4 (quat C), 37.1 (CH), 28.1 (CH_2), 16.0 (CH_3), 14.2 (CH_3); Anal. calc. for $C_{18}H_{18}N_4O_3$, C 63.89, H 5.36, N 16.56. Found: C 64.46, H 5.41, N 18.71.

*2.1.6 Synthesis of ethyl 6-amino-5-cyano-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1e**)*. Following the above mentioned procedure, **1e** was isolated as a yellowish solid 75%, mp 235-237 °C; IR *v* cm^{-1}: 3357 (NH_2), 3155 (NH), 2195 (CN), 1723 (COOEt), 1631 (C=C); δ_H (DMSO, 400 MHz): 8.14 (dt, J = 9.3, 2.3 Hz, 2H, Ar H), 7.36 (dt, J = 9.1, 2.3 Hz, 2H, Ar H), 7.20-7.11 (s, 2H, NH_2), 4.92 (s, 1H, CH), 4.03 (q, J = 7.0 Hz, 2H, CH_2), 1.00 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (DMSO, 100 MHz): 160.7 (CNH_2), 158.4 (C=O), 152.7 (CNH), 146.7 (quat. Ar C), 129.5 (quat. C), 129.3 (Ar C), 124.1 (Ar C), 120.4 (CN), 102.7 (quat. C), 61.5 (CH_2), 57.0 (quat. C), 37.1 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{13}N_5O_5$, C 54.09, H 3.69, N 19.71. Found: C 54.22, H 3.60, N 22.71.

*2.1.7 Synthesis of ethyl 6-amino-5-cyano-4-(3-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1f**)*. Following the above mentioned procedure, **1f** was isolated as a yellowish solid 83%, m.p 224-225 °C; IR *v* cm^{-1}: 3432 (NH_2), 3183 (NH), 2189 (CN), 1713 (COOEt), 1635 (C=C). δ_H (DMSO, 400 MHz): 10.30-9.99 (s, 1H, Ar H), 7.18-7.13 (m, 1H, Ar H), 7.05-6.97 (s, 2H, NH_2), 6.86-6.79 (m, 2H, Ar H), 4.63 (s, 1H, CH), 4.08 (q, J = 7.0 Hz, 2H, CH_2), 1.08 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (DMSO, 100 MHz): 160.7 (CNH_2), 158.4 (C=O), 155.9 (CNH), 148.1 (quat. Ar C), 147.5 (quat. Ar C), 134.9 (Ar C), 130.5 (Ar C), 129.8 (quat. C), 122.4 (Ar C), 120.5 (CN), 102.8 (quat. C), 61.5 (CH_2), 57.3 (quat. C), 36.9 (CH), 14.2 (CH_3); Anal. calc. for $C_{16}H_{13}N_5O_5$, C 53.92, H 3.62, N 22.51. Found: C 54.09; H 3.69, N 19.71.

*2.1.8 Synthesis of ethyl 6-amino-4-(4-bromophenyl)-5-cyano-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1g**)*. Following the above mentioned procedure, **1g** was isolated as a white solid 73%, m.p 221-222 °C. IR *v* cm^{-1}: 3400 (NH_2), 3174 (NH), 2189 (CN), 1770 (COOEt), 1637 (C=C). δ_H (DMSO, 400 MHz): 7.45-7.43 (m, 2H, Ar H), 7.05-7.01 (m, 4H, NH_2 Ar H), 4.72 (s, 1H, CH), 4.06 (q, J = 6.9 Hz, 2H, CH_2),1.03 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.5 (CNH_2), 158.6 (C=O), 156.0 (CNH), 144.8 (quat. Ar), 131.6 (Ar C), 130.1 (Ar C), 129.6 (quat C), 120.6 (CN), 103.5 (quat C), 61.4 (CH_2), 57.8 (quat. C), 36.9 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{13}BrN_4O_4$, C 47.43, H 3.23, N 13.83. Found: C 47.18, H 3.15, N 15.28.

*2.1.9 Synthesis of ethyl 6-amino-5-cyano-4-(4-hydroxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1h**)*. Following the above mentioned procedure, **1h** was isolated as a white solid 57%, m.p 217-218 °C. IR *v* cm^{-1}: 3406 (NH_2), 3222 (NH), 2273 (CN), 1731 (COOEt), 1650 (C=C). δ_H (DMSO, 400 MHz): 9.25 (s, 1H, OH), 6.91 (s, 2H, NH_2), 6.84 (dd, J = 6.4, 1.8 Hz, 2H, Ar H), 6.61 (dd, J = 6.4, 1.8 Hz, 2H, Ar H), 4.59 (s, 1H, CH), 4.07 (q, J = 7.2 Hz, 2H, CH_2), 1.06 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.3 (CNH_2), 158.7 (C=O), 156.4 (CNH), 156.0 (quat. Ar C), 135.9 (quat. Ar C), 129.4 (quat. C), 128.8 (Ar C), 120.9 (CN), 115.4 (Ar C), 104.8 (quat. C), 61.3 (CH_2), 58.8 (quat. C), 36.7 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{14}N_4O_4$, C 58.89, H 4.32, N 17.70. Found: C 58.91, H 4.31, N 19.73.

*2.1.10 Syntheis of ethyl 6-amino-4-(3-bromo-4-hydroxyphenyl)-5-cyano-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1i**)*. Following the above mentioned procedure, **1i** was isolated as a white solid 73%, m.p 224-225 °C; IR *v* cm^{-1}: 3402 (NH_2), 3320 (NH), 2196 (CN), 1712 (COOEt), 1644 (C=C). δ_H (DMSO, 400 MHz): 8.10-8.04 (m, 1H, Ar H), 7.93 (s, 1H, OH), 7.61-7.54 (m, 2H, Ar H), 7.16 (s, 2H, NH_2), 4.98 (s, 1H, CH), 4.03 (q, J = 7.2 Hz, 2H, CH_2), 0.98 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C (DMSO, 100 MHz): 160.4 (CNH_2), 158.6 (C=O), 155.8 (CNH), 153.1 (quat. Ar C), 137.7 (quat Ar C), 132.1 (Ar C), 129.5 (quat C), 128.1 (Ar C), 120.8 (CN), 116.7 (quat Ar C), 109.1 (quat. C), 104.0 (quat C), 61.4 (CH_2), 58.2 (quat. C), 36.3 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{13}BrN_4O_4$, C 47.43, H 3.23, N 13.83. Found: C 47.18, H 3.15, N 15.28.

*2.1.11 Synthesis of ethyl 6-amino-4-(3-chloro-4-hydroxyphenyl)-5-cyano-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1j**)*. Following the above mentioned procedure, **1j** was isolated as a white solid 50%, m.p 227-229 °C; IR *v* cm^{-1}: 3406 (NH_2), 3319 (NH), 2202 (CN), 1701 (COOEt), 1649 (C=C). δ_H (DMSO, 400 MHz): 10.04 (s, 1H, OH), 7.05-6.98 (m, 3H, NH_2 Ar H), 6.86-6.78 (m, 2H, Ar H), 4.63 (s, 1H, CH), 4.08 (d, J = 7.1 Hz, 2H, CH_2), 1.07 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.4 (CNH_2), 158.6 (C=O), 152.1 (CNH), 152.1 (quat. Ar C), 137.4 (quat. Ar C), 129.5 (quat C), 129.2 (Ar C), 127.4 (Ar

C), 120.8 (CN), 119.4 (quat. Ar C), 117.0 (Ar C), 104.0 (quat C), 61.4 (CH_2), 58.2 (quat. C), 36.4 (CH), 14.3 (CH_3); Anal. calc. for $C_{16}H_{13}ClN_4O_4$, C 53.27, H 3.63, N 15.53. Found: C 53.02, H 3.57, N 17.43.

*2.1.12 Synthesis of ethyl 6-amino-5-cyano-4-(4-cyanophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1k**)*. Following the above mentioned procedure, **1k** was isolated as a yellowish solid 74%, m.p 218-221 °C; IR *v* cm^{-1}: 3386 (NH_2), 3214 (NH), 2233 (CN), 1713 (COOEt), 1650 (C=C). δ_H (DMSO, 400 MHz): 7.73 (dd, J = 6.4, 1.8 Hz, 2H, Ar H), 7.27 (dd, J = 6.4, 1.8 Hz, 2H, (Ar H), 7.12 (s, 2H, NH_2), 4.85 (s, 1H, CH), 4.03 (q, J = 7.0 Hz, 2H, CH_2), 0.98 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.6 (CNH_2), 158.4 (C=O), 156.0 (CNH),150.7 (quat. Ar C), 132.9 (Ar C), 129.7 (quat C), 129.0 (Ar C), 120.5 (CN), 119.3 (quat. Ar C), 102.8 (quat. C), 61.4 (CH_2), 57.2 (quat. C), 37.4 (CH), 14.3 (CH_3); Anal. calc. for $C_{17}H_{13}N_5O_3$, C 60.89, H 3.91, N 20.89. Found: C 62.02, H 3.83, N 24.32.

*2.1.13 Synthesis of ethyl 6-amino-5-cyano-4-(furan-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1l**)*. Following the above mentioned procedure, **1l** was isolated as a yellowish solid 63%, m.p 216-218 °C; IR *v* cm^{-1}: 3404 (NH_2), 3298 (NH), 2192 (CN), 1713 (COOEt), 1644 (C=C). δ_H (DMSO, 400 MHz): 7.44 (q, J = 0.9 Hz, 1H, Ar H), 7.08 (s, 2H, NH_2), 6.31 (q, J = 1.7 Hz, 1H, Ar H), 6.07 (d, J = 2.7 Hz, 1H, Ar H), 4.88 (s, 1H, CH), 4.14 (d, J = 7.1 Hz, 2H, CH_2), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 161.3 (CNH_2), 158.7 (C=O), 156.0 (CNH), 155.9 (quat. Ar C), 142.4 (Ar C), 129.7 (Ar C), 120.6 (CN), 110.8 (Ar C), 105.9 (quat C), 61.4 (CH_2), 55.2 (quat. C), 31.2 (CH), 14.3 (CH_3). Anal. calc. for $C_{14}H_{12}N_4O_4$, C 56.00, H 4.03, N 18.66. Found: C 56.29, H 4.04, N 21.32.

*2.1.14 Synthesis of ethyl 6-amino-5-cyano-4-(thiophen-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1m**)*. Following the above mentioned procedure, **1m** was isolated as a yellowish solid 65%, m.p 205-207 °C; IR *v* cm^{-1}: 3402 (NH_2), 3256 (NH), 2203 (CN), 1729 (COOEt), 1627 (C=C). δ_H (DMSO, 400 MHz): 7.28 (m, 1H, Ar H), 7.10 (s, 2H, NH_2), 6.88-6.86 (m, 2H, Ar H), 5.08 (s, 1H, CH), 4.16-4.11 (m, 2H, CH_2), 1.13 (t, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 160.7 (CNH_2), 158.6 (C=O), 155.4 (CNH), 141.0 (quat Ar C), 129.7 (Ar C), 127.1 (Ar C), 124.7 (Ar C), 120.7 (CN), 104.2 (quat C), 61.5 (CH_2), 58.2 (quat. C), 32.6 (CH), 14.3 (CH_3). Anal. calc. for $C_{14}H_{12}N_4O_3S$, C 53.16, H 3.82, N 17.71, S 10.14. Found: C 54.35, H 3.61, N 20.21, S 11.43.

*2.1.15 Synthesis of ethyl 6-amino-5-cyano-4-ethyl-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1n**)*. Following the above mentioned procedure, **1n** was isolated as a yellowish solid 90%, m.p 180-182 °C; IR *v* cm^{-1}: 3421 (NH_2), 3178 (NH), 2192 (CN), 1712 (COOEt), 1633 (C=C). δ_H (DMSO, 400 MHz): 6.91 (s, 2H, NH_2), 4.32-4.22 (m, 2H, CH_2), 3.72 (t, J = 4.1 Hz, 1H, CH), 1.87-1.74 (m, 1H, CH), 1.66-1.53 (m, 1H, CH), 1.27 (t, J = 7.1 Hz, 3H, CH_3), 0.60 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 162.2 (CNH_2), 159.0 (C=O), 156.6 (CNH), 121.2 (CN), 103.8 (quat C), 96.9 (quat. C), 61.6 (CH_2), 54.7 (quat. C), 31.9 (CH), 28.0 (CH_2), 14.5 (CH_3), 8.78 (CH_3); Anal. calc. for $C_{12}H_{14}N_4O_3$, C 54.96, H 5.38, N 21.36. Found: C 53.85, H 5.57, N 24.16.

*2.1.16 Synthesis of ethyl 6-amino-5-cyano-4-isopropyl-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1o**)*. Following the above mentioned procedure, **1o** was isolated as a yellowish solid 91%, m.p 200-201 °C; IR *v* cm^{-1}: 3427 (NH_2), 3178 (NH), 2192 (CN), 1712 (COOEt), 1633 (C=C). δ_H (DMSO, 400 MHz): 6.98 (s, 2H, NH_2), 4.26 (dtd, J = 18.7, 7.1, 3.7 Hz, 2H, CH_2), 3.57 (d, J = 2.7 Hz, 1H, CH), 2.00 (td, J = 7.0, 3.0 Hz, 1H,C*H*H), 1.27 (t, J = 7.1 Hz, 3H, CH_2 H), 0.93 (d, J = 6.9 Hz, 3H, CH_3), 0.57 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 163.5 (CNH_2), 159.1 (C=O), 156.9 (CNH), 128.7 (quat. C), 122.3 (CN), 105.2 (quat C), 61.5 (CH_2), 51.6 (quat C), 37.6 (CH), 35.4 (CH), 20.7, 17.1 (CH_3), 14.4 (CH_3); Anal. calc. for $C_{13}H_{16}N_4O_3$, C 56.51, H 5.84, N 20.28. Found: C 56.18, H 5.85, N 21.93.

*2.1.17 Synthesis of ethyl 6-amino-5-cyano-4-heptyl-1,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (**1p**)*. Following the above mentioned procedure, **1p** was isolated as a yellowish solid 11%, m.p 204-206 °C; IR *v* cm^{-1}: 3427 (NH_2), 3178 (NH), 2192 (CN), 1712 (COOEt), 1633 (C=C). δ_H (DMSO, 400 MHz): 6.89 (s, 2H, NH_2), 4.27 (dtd, J = 24.2, 7.1, 3.7 Hz, 2H, CH_2), 3.70 (dd, J = 4.8, 3.9 Hz, 1H, CH), 1.82-1.69 (m, 1H, CH*H*), 1.63-1.50 (m, 1H, C*H*H), 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.21-1.06 (m, 9H, 4XCH_2H), 1.00 (m, 1H, CH*H*), 0.78 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 162.0 (CNH_2), 159.0 (C=O), 156.4 (CNH), 129.0 (quat. C), 121.2 (CN), 104.5 (quat. C), 61.5 (CH_2), 55.2 (quat. C), 35.8 (CH), 31.6 (CH), 31.1 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 24.0 (CH_2), 22.5 (CH_2), 14.5 (CH_3), 14.4 (CH_3); Anal. calc. for $C_{17}H_{24}N_4O_3$, C 61.43, H 7.28, N 16.86. Found: C 61.44, H 7.22, N 19.42.

*2.1.18 Synthesis of ethyl 6-amino-5-cyano-2',3',5',6'-tetrahydro-1H-spiro[pyrano[2,3-c]pyrazole-4,4'-thiopyran]-3-carboxylate (**1q**)*. Following the above mentioned procedure, **1q** was isolated as a yellowish solid 19%, δ_H (DMSO, 400 MHz): 6.85 (s, 2H, NH_2), 4.31 (q, J = 7.2 Hz, 2H, CH2), 3.48 (td, J = 13.7, 2.3 Hz, 2H, CH_2), 2.69-2.60 (td, J = 13.5, 4.5 Hz, 2H, CH_2), 2.40 (d, J = 13.7 Hz, 2H, CH_2), 1.92 (d, J = 13.7 Hz, 2H, CH_2), 1.31 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 161.5 (CNH_2), 158.7 (C=O), 154.6 (CNH), 129.1 (quat. C), 124.5 (CN), 110.3 (quat. C), 61.9 (CH_2), 59.0 (quat. C), 33.2 (CH_2), 23.4 (3XCH_2), 14.63 (CH_3); Anal. calc. for $C_{14}H_{16}N_4O_3S$, C 52.49, H 5.03, N 17.49, S 10.01. Found: C 52.49, H 5.07, N 22.06, S 12.62.

2.1.19 Synthesis of *ethyl 6'-amino-5'-cyano-1-methyl-1'H-spiro[piperidine-4,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate* (***1r***). Following the above mentioned procedure, **1r** was isolated as a yellowish solid 23%, mp. 200-202. δ_H (DMSO, 400 MHz): 6.82 (2H), 4.30-4.33 (2H), 2.78-2.60 (2H), 2.51-2.41 (2H), 2.00-1.96 (2H), 1.29-1.25 (3H). ^{13}C (DMSO, 100 MHz): 14.1, 20.4, 33.0, 50.6, 68.5, 117.3, 119.0, 136.4, 158.9, 161.7.

*2.1.20 Synthesis of ethyl 6'-amino-5'-cyano-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3'-carboxylate (**1s**)*. Following the above mentioned procedure, **1s** was isolated as a yellowish solid 69%, m.p 270-271 °C; IR *v* cm^{-1}: 3371 (NH_2), 3165 (NH), 2187 (CN), 1713 (COOEt), 1648 (C=C). δ_H (DMSO, 400 MHz): 10.55 (s, 1H, NH), 7.25 (s, 2H, NH_2), 7.16 (td, J = 7.5, 1.4 Hz, 1H, Ar H), 6.93-6.80 (m, 3H, Ar H), 3.94-3.82 (m, 2H. CH_2), 0.88 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C (DMSO, 100 MHz): 178.0 (C=O), 161.5 (CNH_2), 158.1 (C=O), 142.6 (CNH), 134.6 (Ar C), 129.0 (Ar C), 124.2 (Ar C), 122.6 (CN), 118.5 (Ar C), 109.8 (quat C), 100.6 (quat C), 61.3 (CH2), 57.3 (quat C), 48.0 (quat C), 14.0 (CH_3); Anal. calc. for $C_{17}H_{13}N_5O_4$, C 58.12, H 3.73, N 19.93. Found: C 57.89, H 3.68, N 22.84.

*2.1.21 Synthesis of ethyl 6-amino-5-cyano-5'-(4-methoxyphenyl)-1'-methyl-2'-oxo-1H-spiro[pyrano[2,3-c]pyrazole-4,3'-pyrrolidine]-3-carboxylate (**1t**)*. Following the above mentioned procedure, **1t** was isolated as a yellowish solid 26%, m.p 212-214 °C; IR *v* cm^{-1}: 3366 (NH_2), 3193 (NH), 2193 (CN), 1733 (COOEt), 1672 (C=C); δ_H (DMSO, 400 MHz): 7.38-7.32 (m, 2H, Ar H), 7.09 (s, 2H, NH_2), 6.94-6.89 (m, 2H, Ar H), 4.70-4.62 (m, 1H, CH), 4.33 (td, J = 7.1 Hz, 2H, CH_2), 3.72 (s, 3H, NCH_3), 2.84 (dd, J = 14.2, 9.1 Hz, 1H, CH*H*), 2.50 (s, 3H, OCH_3), 1.99 (dd, J = 14.2, 6.9 Hz, 1H, C*H*H), 1.28 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 173.8 (C=O), 161.0 (CNH_2), 159.4 (quat. Ar C), 158.5 (C=O), 155.6 (quat. C), 133.8 (quat. Ar C), 128.9 (quat. C), 128.0 (Ar C), 120.5 (CN), 114.6 (Ar C), 105.2 (quat. C), 62.0 (CH_2), 61.3 (CH), 60.9 (quat. C), 55.6 (NCH_3), 40.4 (CH_2), 40.2 (quat. C), 29.3 (OCH_3), 14.6 (CH_3); Anal. calc. for $C_{21}H_{21}N_5O_5$, C 59.57, H 5.00, N 16.54. Found: C 59.72, H 5.20, N 18.96.

*2.2.22 Synthesis of diethyl 6-amino-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-3,5-dicarboxylate (**2a**)*. A mixture of ethyl 5-hydroxy-1*H*-pyrazole-3-carboxylate (0.21 g, 1 mmol) and (*Z*)-ethyl 2-cyano-3-phenylacrylate (0.20 g, 1 mmol) in ethanol (6 ml) containing catalytic amount of triethylamine (0.01 ml, 0.2 mmol) was refluxed for 2 h (monitored by TLC). After the reaction was completed, the mixture was left to cool to room temperature and evaporated to produce white solid. The crude product was recrystallized in methanol to produce diethyl 6-amino-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-3,5-dicarboxylate **2a** (0.06 g, 20%) as white crystal; δ_H (DMSO, 400 MHz): 7.77 (s, 2H, NH_2), 7.19-7.13 (m, 2H, Ar H), 7.09-7.02 (m, 3H, Ar H), 4.98 (s, 1H, CH), 4.17 (q, J = 7.2 Hz, 2H, CH_2), 3.91 (q, J = 7.0 Hz, 2H, CH_2), 1.18 (t, J = 7.1

Hz, 3H, CH_3), 1.04 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 168.9 (C=O), 161.6 (CNH_2), 158.8 (C=O), 156.0 (CNH), 147.4 (quat. Ar C), 128.9 (quat. C), 128.3 (Ar C), 128.1 (Ar C), 126.3 (Ar C), 107.5 (quat C), 77.7 (quat. C), 61.4 (CH_2), 59.3 (CH_2), 35.7 (CH), 14.6 (CH_3), 14.5 (CH_3); Anal. calc. for $C_{18}H_{19}N_3O_5$, C 60.50, H 5.36, N 11.76. Found: C 60.71, H 5.34, N 11.78.

*2.2.23 Synthesis of diethyl 6'-amino-2-oxo-1'H-spiro[indoline-3,4'-pyrano[2,3-c]pyrazole]-3',5'-dicarboxylate (**2c**).* A mixture of ethyl 5-hydroxy-1*H*-pyrazole-3-carboxylate (0.21 g, 1 mmol) and (*E*)-ethyl 2-cyano-2-(2-oxoindolin-3-ylidene)acetate (0.24 g, 1 mmol) in ethanol (6 ml) containing catalytic amount of triethylamine (0.01 ml, 0.2 mmol) was refluxed for 2 h (monitored by TLC). After the reaction was completed, the mixture was left to cool to room temperature to produce white solid. The crude product was recrystallized in methanol to produce diethyl 6'-amino-2-oxo-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3',5'-dicarboxylate, **2c** (0.40 g, 84%) as white crystal; δ_H (DMSO, 400 MHz) 10.31 (s, 1H, NH), 8.05 (s, 2H, NH_2), 7.05 (td, J = 7.2, 2.0 Hz, 1H, Ar H), 6.77-6.71 (m, 3H, Ar H), 4.38-4.31 (1H), 3.97 (td, J = 7.1, 3.7 Hz, 2H, CH_2), 3.73-3.63 (m, 2H, CH_2), 1.01 (t, J = 6.9 Hz, 3H, CH_3), 0.74 (t, J = 7.1 Hz, 3H, CH_3); Anal. calc. for $C_{19}H_{18}N_4O_6$, C 57.28, H 4.55, N 14.06. Found: C 57.35, H 4.97, N 13.37.

*2.2.24 Synthesis of ethyl 6'-amino-1'-(benzo[d]thiazol-2-yl)-5'-cyano-2-oxo-1'H-spiro[indoline-3,4'-pyrano [2,3-c]pyrazole]-3'-carboxylate (**2d**).* To a solution of diethyloxalacetate sodium salt (0.23 g, 1.1 mmol) in 10 ml ethanol was added 2-hydrazinothiazole (0.18 g, 1.1 mmol) and 1 ml of acetic acid and refluxed for 15 minutes. Isatin (0.15 g, 1 mmol) and malononitrile (0.06 g, 1 mmol) were then added to the reaction mixture, and heating was continued for additional 30 minutes. The reaction mixture was left to cool and the resulting solid was filtered off and washed with water and diethylether to obtain yellowish solid, **2d** (0.16 g, 32%); m.p 270-271 °C. IR ν cm^{-1}: 3446 (NH_2), 3347 (NH), 2200 (CN), 1709 (COOEt), 1657 (C=C). δ_H (400 MHz, DMSO-D6): 10.65 (s, 1H, NH), 8.14 (d, J = 7.8 Hz, 1H, Ar H), 7.98 (d, J = 8.2 Hz, 1H, Ar H), 7.61 (s, 2H, NH_2), 7.58 (dd, J = 8.5, 1.1 Hz, 1H, Ar H), 7.52-7.47 (m, 1H, Ar H), 7.19 (td, J = 7.5, 1.2 Hz, 1H, Ar H), 7.12 (d, J = 7.3 Hz, 1H, Ar H), 6.93-6.84 (m, 2H, Ar H), 3.94 (q, J = 7.1 Hz, 2H, CH_2), 0.94 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (100 MHz, DMSO): 177.6 (C=O), 160.1 (CNH_2), 159.7 (C=O), 157.9 (quat. C), 150.8 (quat. C), 147.8 (quat. Ar C), 142.7 (quat Ar C), 140.7 (quat. Ar C), 133.8 (quat Ar C), 133.1 (quat C), 129.4 (Ar C), 127.7 (Ar C), 126.5 (Ar C), 124.6 (Ar C), 123.3 (Ar C), 122.6 (Ar C), 117.7 (CN), 110.0 (Ar C), 100.4 (quat. C), 61.5 (CH_2), 58.6 (quat. C), 48.2 (quat C), 14.1 (CH_3); Anal. calc. for $C_{24}H_{16}N_6O_4S$, C 59.50, H 3.33, N 17.35, S 6.62. Found: C 59.60, H 3.31, N 17.42, S 6.97.

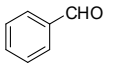
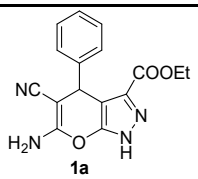
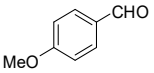
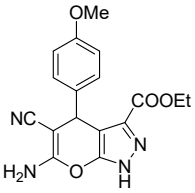
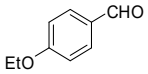
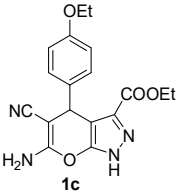
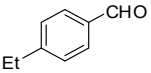
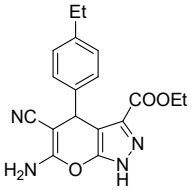
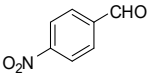
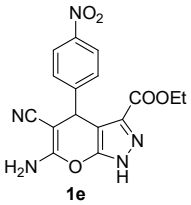
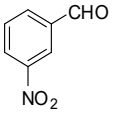
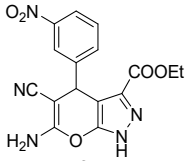
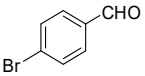
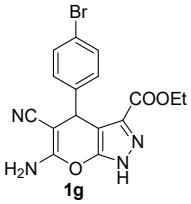
2.2.25 Synthesis of ethyl 6'-amino-5'-cyano-2-oxo-1'-(pyridin-2-yl)-1'*H*-spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole]-3'-carboxylate *(**2e**).* To a solution of diethyloxalacetate sodium salt (0.23 g, 1.1 mmol) in 10 ml ethanol was added 2-hydrazinopyridine (0.12 g, 1.1 mmol) and 0.5 ml of acetic acid and refluxed for 15 minutes. Isatin 14 (0.15 g, 1 mmol) and malononitrile (0.06 g, 1 mmol) were then added to the reaction mixture, and heating was continued for additional 30 minutes. The reaction mixture was left to cool and the resulting solid was filtered off and washed with water and diethylether to obtain **2e** as white solid (0.15 g, 34%); m.p 270-271 °C; IR ν cm^{-1}: 3440 (NH_2), 3312 (NH), 2201 (CN), 1705 (COOEt), 1656 (C=C). δ_H (DMSO, 400 MHz): 10.60 (s, 1H, NH), 8.60 (m, 1H, Ar H), 8.09 (m, 1H, Ar H), 7.82 (d, J = 8.2 Hz, 1H, Ar H), 7.54 (m, 1H, Ar H), 7.43 (s, 2H, NH_2), 7.18 (m, 1H, Ar H), 7.04 (d, J = 6.9 Hz, 1H, Ar H), 6.92-6.83 (m, 2H, Ar H), 3.97-3.85 (m, 2H, CH_2), 0.93 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C (DMSO, 100 MHz): 177.9 (C=O), 160.3 (CNH_2), 149.8 (C=O), 149.3 (Ar C), 147.2 (CNH), 142.7(quat. Ar C), 140.3 (Ar C), 139.2 (quat. Ar C), 134.2 (quat. C), 129.2 (Ar C), 124.7 (Ar C), 124.4 (Ar C), 122.5 (Ar C), 117.9 (CN), 117.8 (Ar C), 109.9 (Ar C), 99.4 (quat. C), 61.0 (CH_2), 58.4 (quat. C), 14.2 (CH_3); Anal. calc. for $C_{22}H_{16}N_6O_4$, C 61.68, H 3.76, N 19.62. Found: C 61.32, H 3.68, N 19.53.

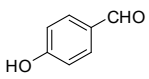
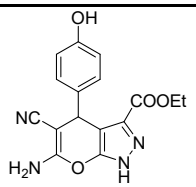
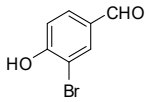
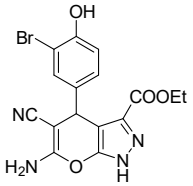
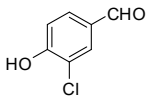
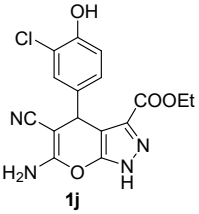
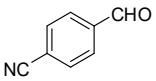
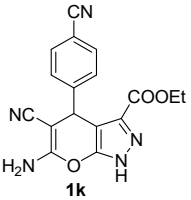
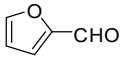
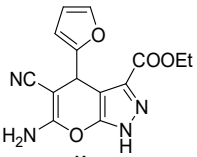
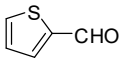
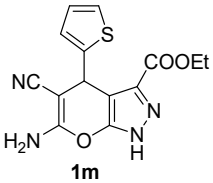
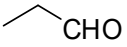
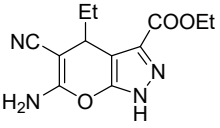
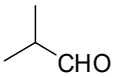
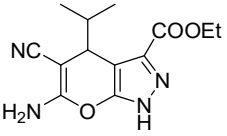
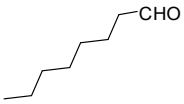
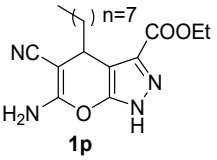
3. Results and Discussion

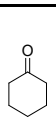
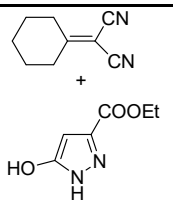
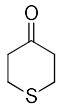
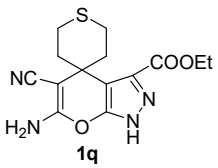
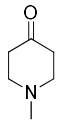
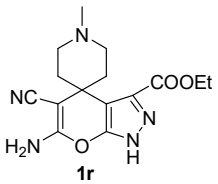
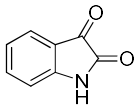
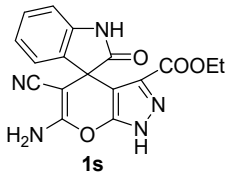
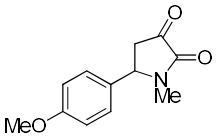
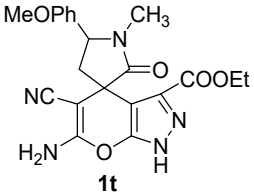
Initially, the reaction was carried out by replicating Gein's protocol of four-component two-parallel reaction manner by using hydrazine hydrate, diethyl oxalacetate, benzaldehyde and malonitrile as our reaction model.[16] Attempts for optimizing synthesis of **1a** by changing the reactants parameters and by adding

different catalysts led to the same desired product with low yields. However, upon changing Gein's protocol to a domino one-pot reaction manner successfully furnished us with the cyclized product **1a** in moderate yield of 82%. To further understand the mechanism of the reaction we then extended this domino four-component cyclization protocol using varieties of aldehydes (aromatic, aliphatic, hetero-aromatic). The details of the cyclized products (**1a-p**) are depicted in Table 1.

Table 1. Synthesis of dihydropyrano[2,3-*c*]pyrazole-3-carboxylates (**1a-t**)

Entry	Carbonyl Compound	Product	Time (min)	Yield (%)	M.p (˚C)
1		 **1a**	30	82	226-227
2		 **1b**	30	65	215-217
3		 **1c**	30	60	210-211
4		 **1d**	30	69	212-213
5		 **1e**	30	75	235-237
6		 **1f**	30	83	224-225
7		 **1g**	30	73	221-223

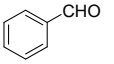
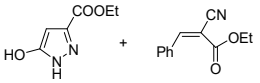
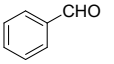
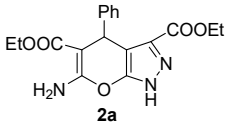
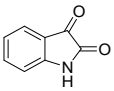
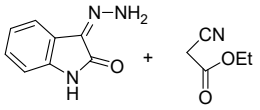
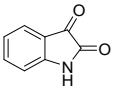
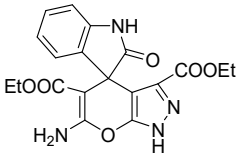
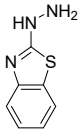
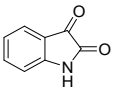
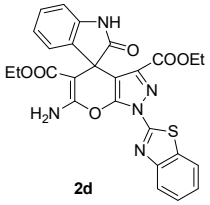
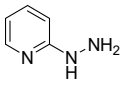
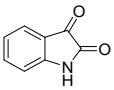
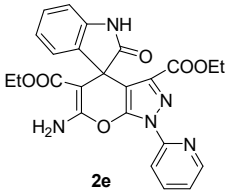
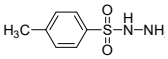
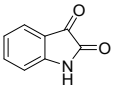
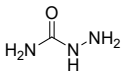
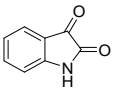
8		 **1h**	30	57	217-218
9		 **1i**	30	73	224-225
10		 **1j**	30	50	228-229
11		 **1k**	30	74	218-221
12		 **1l**	30	63	216-218
13		 **1m**	30	65	205-207
14		 **1n**	30	90	180-182
15		 **1o**	30	91	190-192
16		 **1p**	30	11	200-203

17			30	-	-
18		 **1q**	30	28	190-191
19		 **1r**	30	32	200-202
20		 **1s**	30	69	270-271
21		 **1t**	30	26	212-214

Aromatic aldehydes bearing electron-withdrawing groups which are nitro, cyano and halogens (Table 1, Entries 5-11) significantly contributed to higher yields (74%-83%) as compared to aromatic aldehyde with electron-donating groups (60%-69%) (Table 1, Entries 2-4). Similarly, hetero-aromatic aldehydes of furan-2-carbaldehyde and thiophene-2-carbaldehyde successfully furnished their cyclized products in reasonable yields of 63% and 65% respectively (Table 1, Entries 12-13). Interestingly, attempts on utilizing aliphatic aldehydes had also furnished alkylated products in good yields. However the product yields were observed to decrease significantly upon increasing the aliphatic chain length (Table 2, Entry 16). Previously, many aliphatic aldehydes were reported to be not suitable as electrophiles in any one-pot procedures due to their tendency to undergo self-Aldol condensation or Cannizzaro-type of reactions.[22]

Further synthetic explorations by employing keto compounds had also successfully furnished us with some novel spiro pyranopyrazoles but again in reasonable yields (Table 1, Entries 18-21). These keto compounds include tetrahydro-4*H*-thiopyran-4one, 1-methylpiperidin-4-one, 5-methoxy-2,3-pyrrolidine-dione and isatin. Nevertheless, it was observed that no pyranopyrazole product was produced upon using cyclohexanone as the source of carbonyl compound; instead, only its corresponding Knoevenegal and pyrazolone products were isolated. The electronic contribution of the Knoevenegal product and its pyrazolone counterpart could be the significant factor towards successful pyranopyrazole cyclization in such domino one-pot reaction.[23] Therefore, an electronic correlation study for the domino one-pot reaction to produce different derivatives of Knoevenegel and pyrazolone products was carried out under the standard domino four-component reaction protocol (Table 2).

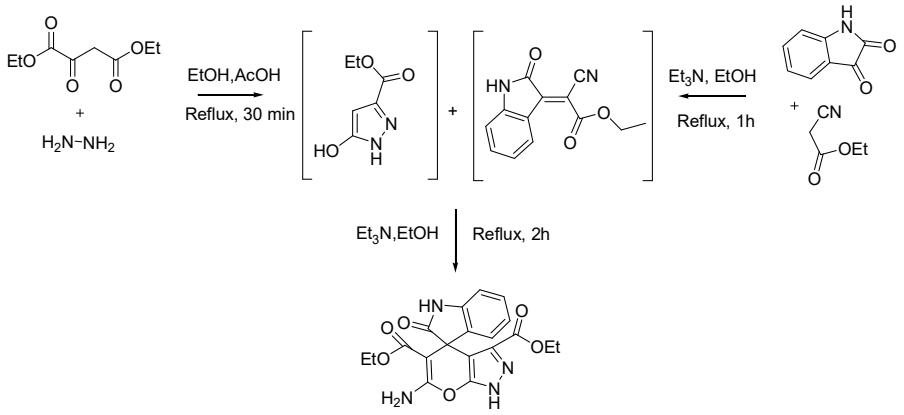
Table 2. Synthesis of pyranopyrazole using hydrazine and malanonitrile derivatives

Entry	Active methylene compound	Hydrazine derivatives	Malononitrile derivatives	Carbonyl compound	Product(s)	Yield (%)
1	Diethyl oxalacetate	NH_2-NH_2				-
2	Diethyl oxalacetate	NH_2-NH_2			 **2a**	20
3	Diethyl oxalacetate	NH_2-NH_2			 **2b**	-
4	Diethyl oxalacetate	NH_2-NH_2			 **2c**	84
5	Diethyl oxalacetate				 **2d**	33
6	Diethyl oxalacetate				 **2e**	34
7	Diethyl oxalacetate				Recovered starting material	-
8	Diethyl oxalacetate				Recovered starting material	-

It was clearly observed that when cyanoester was used as the malanonitrile derivative, no pyranopyrazole product was obtained. Instead, only intermediates of Knoevenegal and pyrazolone products were isolated (Table 2, Entry 1). Conversely, when isatin was employed in the reaction, different nucleophilic-addition product (**2b)** was identified (Table 2, Entry 3). Since ketones are less electrophilic than aldehyde, a competition between hydrazine and cyanoester as the nucleophile was expected. To overcome this problem, different parallel two-step reactions by reacting the pre-synthesized Knoevenegal and pyrazolone products was suggested (Scheme 1). In addition, a catalytic amount of base (Et_3N) was also added into the reaction mixture. Bases are needed to deprotonate the acidic proton of the cyanoester and to induce the Michael addition reaction. No reaction would take place without the presence of bases in the reaction.

Interestingly, combination of reaction using isatin and cyanoester successfully gave compound **2c** (84%) in this new parallel two-step one-pot reaction. High yield of product **2c** justify the compatibility of the

Michael reaction in the reaction, perhaps due to the carbonyl activation in the Knoevenegal isatin intermediate with the pyrazolone. However, using benzaldehyde as the carbonyl compound, the cyclized product **2a** was obtained in low yields (20%) despite all attempts on adding bases and prolonging the reaction time (Table 2, Entries 2,4).



Scheme 1. Parallel two-step one-pot reaction

Finally, in order to validate the electronic contribution of the pyrazolone intermediate towards pyranopyrazole cyclization, derivatives of pyrazolone were prepared by utilizing different hydrazine derivatives, namely 2-hydrazinopyridine, 2-hydrazinothiazole, *p*-toluenesulfonyl hydrazine and semicarbazide (Table 2, Entries 3-6). It was observed that using *p*-toluenesulfonyl hydrazine and semicarbazide with strong electron withdrawing group did not give the cyclized products. On the contrary, 2-hydrazinopyridine and 2-hydrazinothiazole managed to give pyranopyrazole products **2d** and **2e**, respectively but in poor yields (33-34%) (Table 2, Entries 5-6). Competition on nucleophilic addition reactions was proposed to take place as multiple spots were observed during TLC analyses which subsequently led to low yields.

An electronic effect on each intermediates of Knoevenegel and pyrazolone contributes to the successful pyranopyrazole cyclization. Bearing electron rich group either on Knoevenegel or pyrazolone will hinder the one-pot reaction. Therefore longer reaction time and addition of bases are needed to successfully led to cyclization. Upon having diverse classes of pyranopyrazole in hand, evaluation on biological activities of this new class of pyranopyrazole as antibiotics are being investigated in our laboratory.

4. Conclusion

In summary, we have developed a salient reaction protocol using domino one-pot, four-component approach towards generating pyranopyrazole-carboxylate type compound. This protocol was found to be applicable for most classes of aromatic or aliphatic aldehydes and ketone and different classes of hydrazine or malononitrile. Consequently, it is useful for the synthesis of a variety of pyranopyrazoles under green catalyst-free multicomponent reaction. It was also observed that electronic effect of the Knoevenegel and pyrazolone intermediates will contribute towards the success of the pyranopyrazole cyclization.

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Supporting Information

Supporting information accompanies this paper on [htttp://www.acgpubs.org/organic-communications](http://www.acgpubs.org/organic-communications)

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