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Reaction of *O*-methylated flavones with semicarbazide: Serendipitous selective demethylation

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Abstract: An unusual reaction of selective demethylation of 5-*O*-methylated flavones, during the reaction with semicarbazide in glacial acetic acid, is reported. The generality of the method was ascertained for various 5-*O*-methylated flavones. However, the method is unsuitable for chalcones, flavanones, aurones, and acetophenones. Four different flavones including heterocyclic flavone were selectively demethylated and the products were characterized by their spectral data.

Keywords: Flavones; semicarbazide; serendipitous; selective demethylation.

1. Introduction

The term flavonoid refers to the compounds having C_6-C_3-C_6 units in their basic skeleton. Flavonoids[1-6] are a group of naturally occurring polyphenols that are widely found in the plant kingdom. Moreover, these are also a large class of plant secondary metabolites derived from the phenylpropanoid pathway. In addition, among the oxygen heterocycles, chalcones and flavonoids occupy a major position.

2. Background

As the demethylation of aryl methyl ethers to the corresponding phenols are very significant reactions in organic synthesis, particularly in natural flavonoids synthesis and still there is a search for an amicable demethylating agent for selectivity. The methods reported for the cleavage of highly stable aryl methyl ethers are use of strong acids or bases such as $AlCl_3$[7-9], BBr_3[10-11], $CeCl_3$[12], methyl magnesium iodide[13-14], alkaline thiolate[15], L-Selectride[16-17] and pyridinium hydrochloride[18] etc. However, some of these methods have one or more drawbacks such as vigorous reaction conditions, prolonged reaction times, use of exotic reagents, cost of the reagent is high, low reaction yields. In

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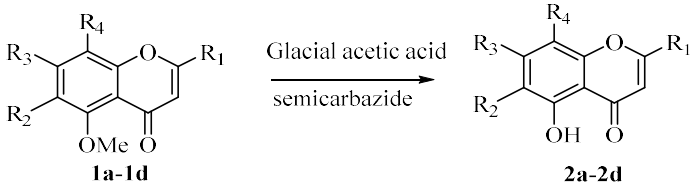
some demethylation procedures preparation of the reagent is also intricate. Moreover, in the most of reported methods for demethylation of aryl methyl ethers, use of large excess amounts of demethylating agents have been generally required and most of the reagents showed mixture of demethylated products for example demethylation of 7-hydroxy-3,5,8-trimethoxyflavones and their acetates with anhydrous aluminum halides in acetonitrile or ether[19] was apparently influenced by both solvents and afforded 5,7-dihydroxy-3,8-dimethoxyflavones in acetonitrile and 3,7-di-hydroxy-5,8-dimethoxyflavones in ether as main products. Aluminium chloride in nitrobenzene and hydrobromic acid which are satisfactory in simpler cases are not suitable for more complex flavanones because they can demethylate other positions also. Further, hydrobromic acid can bring about ring isomeric change. Aqueous hydrochloric acid, which has been used in the case of furanochromones and isoflavones, has not been successful in the partial demethylation of flavanones. Basing on the literature review, the unexpected result provided a highly desirable, cost effective and efficient procedure for selective demethylation of flavones at C5 position as shown in below Scheme 1.



1a-1d **2a-2d**

1a = 2a: R_1= furan, R_2 = R_4 = H, R_3 = OMe
1b = 2b: R_1= 4-OMePh, R_2 = R_4 = H, R_3 = OMe
1c = 2c: R_1= 3,4 di-OMePh, R_2 = R_4 = H, R_3 = OMe
1d = 2d: R_1= 4-OMePh, R_2 = R_4 = Me, R_3 = OMe

Scheme 1. Demethylation of various methylflavones

3. Experimental

General: All the reactions were carried out in oven dried glassware (120 ºC) under atmosphere of nitrogen. Chemicals and solvents are laboratory grade (Merck) and are used as such. All the reactions were monitored by thin layer chromatography (TLC) on percolated plates (silicagel 60 F_{254}) which was purchased from Merck. All the yields refer to isolated products. Proton NMR spectra were recorded on Bruker AMX 400 MHz Spectrometer by the use of deuterated dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard. Proton NMR chemical shifts were referenced to residual protonated solvents (δ 2.5 ppm for DMSO-*d6*) and moisture in DMSO-*d6* (δ 3.3 ppm for moisture in DMSO-*d6*). Carbon-13 NMR spectra were obtained on a Bruker AMX 100 MHz NMR Spectrometer by the use of DMSO as solvent and TMS as internal standard.

*General Procedure for the Synthesis of Demethylated Flavones: 2-Furan-2-yl-5-hydroxy-7-methoxychromen-4-one **(2a)*****:** A solution of 2-Furan-2-yl-5,7-dimethoxychromen-4-one **(1a)** (250 mg, 0.96 mmol) and semicarbazide (73 mg, 0.96 mmol) in glacial acetic acid (5 mL) was stirred for about 24 hrs at reflux temperatures and the progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was poured into ice cold water (50 mL) and then extracted with ethyl acetate (2x25 mL). After evaporation of the solvent, the residue was subjected to column chromatography and the product (**2a**)[20] was obtained with ethylacetate/ hexane solvent system (20:80).

*2-Furan-2-yl-5-hydroxy-7-methoxychromen-4-one **(2a)*****:** Yield 142 mg, 60%.MP: 153-155 ºC.^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.84 (s, 1H), 8.12 (s, 1H), 7.48 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 7.1 Hz, 1H), 6.70 (d, *J* = 7.1 Hz, 1H), 6.42 (d, *J* = 7.1 Hz, 1H), 3.90 (s, 3H).^{13}C NMR (100 MHz, DMSO-*d6*): δ 181.2, 165.3, 161.2, 156.8, 155.3, 147.4, 144.9, 114.6, 113.1, 104.8, 102.9, 98.1, 92.6, 56.06. MS:

*m/*z 259 $[M+1]^+$ mass-258. M.F.Anal. Calcd for$C_{14}H_{10}O_5$ C, 65.12, H, 3.90%; Found: C, 65.15, H, 3.92%.

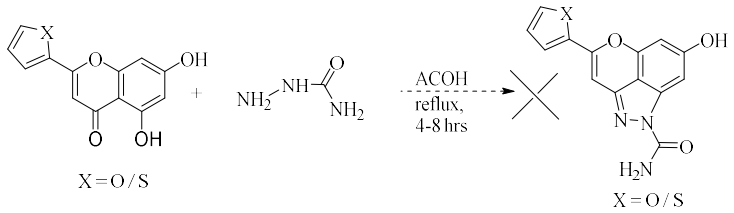
5-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-chromen-4-one **(2b)** [21,22]**:**Yield 143 mg, 60%.MP: 143-145 ^oC. ^1H NMR (400 MHz, DMSO-*d6*): δ 12.9 (s, 1H), 8.03 (d, *J* = 8.04 Hz, 2H), 7.09 (d, *J* = 8.04 Hz, 2H), 6.9 (s, 1H), 6.76 (s, 1H), 6.36 (s, 1H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ 181.9, 171.9, 165.1, 163.6, 162.4, 161.1, 157.2, 128.3, 122.6, 114.5, 104.7,103.6, 97.9, 92.6, 56.0. MS: *m/*z 299 $[M+1]^+$ mass-298. M.F. $C_{17}H_{14}O_5$. Calculated C, 68.45, H, 4.73%; Found: C, 68.50, H, 4.71%.

2-(3,4-dimethoxyphenyl)-5-hydroxy-7-methoxy-chromene-4-one **(2c)**[23,24]**:**Yield**:** 155 mg, 65%.MP: 143-145 ^oC. ^1H NMR (400 MHz, DMSO-*d6*): δ 12.89 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 6.72 (s, 1H), 6.32 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 181.8, 165.1, 163.5, 161.1, 157.1, 152.2, 149.0, 122.7, 120.0, 111.6, 109.4, 104.6, 103.9, 97.9, 92.6, 55.9, 55.8, 55.7. MS: *m/*z 329 $[M+1]^+$ Mass-328. M.F. $C_{18}H_{16}O_6$. Calculated C, 65.85, H, 4.91%; Found: C, 65.87, H, 4.95%.

5-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-6,8-dimethylchromen-4-one **(2d)**[25,26]**:** Yield**:** 151 mg, 63%. M.P. 149-151 ^oC. ^1H NMR(400 MHz, DMSO-*d6*): δ 13.04 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.18-7.09 (m, 2H), 6.99 (s, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 2.35 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 182.69, 163.6, 162.4, 162.2, 156.3, 152.3, 128.3, 122.9, 114.7, 113.1, 108.7, 106.6, 103.5, 60.3, 55.67, 8.3, 8.0. MS: *m/*z 327 $[M+1]^+$ mass-326. M.F. $C_{19}H_{18}O_5$. Calculated C, 69.93, H, 5.56%; Found: C, 69.96, H, 5.53%.

4. Present Study

The present study is a part of our research project mainly aimed to condense some heterocyclic flavones with semicarbazide to produce some fused heterocyclic systems as shown in Scheme 2. The reaction is initiated with equimoles of flavone and semicarbazide in glacial acetic acid at reflux temperatures. The reaction seems to be proceeded as monitered by TLC, and after completion of the staring material the product was isolated. A close look at the spectral data of the final product showed the absence of expected compound but the data confirmed a serendipitous selective monodemethylated flavone which is highly enviable.

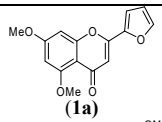
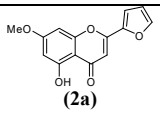
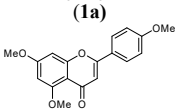
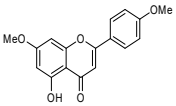
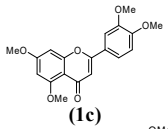
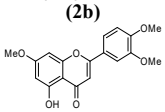
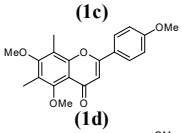
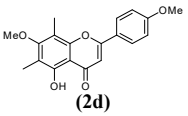
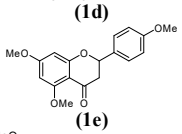
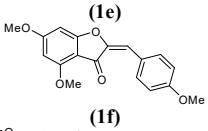
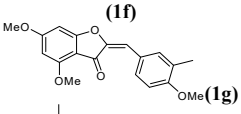
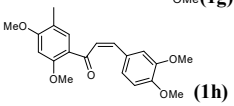
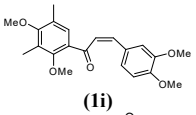
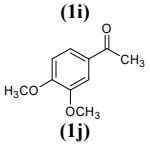
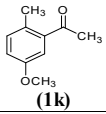


Scheme 2. Condensation of heterocyclic flavones with semicarbazide.

So, in the communication, we wish to report the efficient selective demethylation of some natural flavonoid related methyl flovones using semicarbazide-glacial acetic acid system. As mentioned above the expected condensed product of 5,7-*O*-dimethylfurfural flavone (**1a**) (1 mmol) with semicarbazide (1 mmol), in glacial acetic acid (5 mL) was a heterocyclic compound. After purification of the product the compound was characterized by spectral analysis such as ^1H NMR, ^{13}C NMR and mass. The careful analysis of these spectra; ^1H NMR spectra showed the broad singlet at 12.9 ppm responsible for the chelated hydroxyl group formed by the demethylation of 5-*O*-methyl group. ^{13}C NMR and mass spectral data also reveals the demethylated product. It clearly showed the demethylated product *i.e* 5-*O*-demethylated flavone (**2a**) is formed (Scheme 1) instead of expected condensed product (Scheme 2). Further, in order to test the generality of the reaction the same reaction

was repeated for three more different flavones (**1b-1d**) and found similar trend in the formation 5-*O*-demethylated products (**2a-2d**).

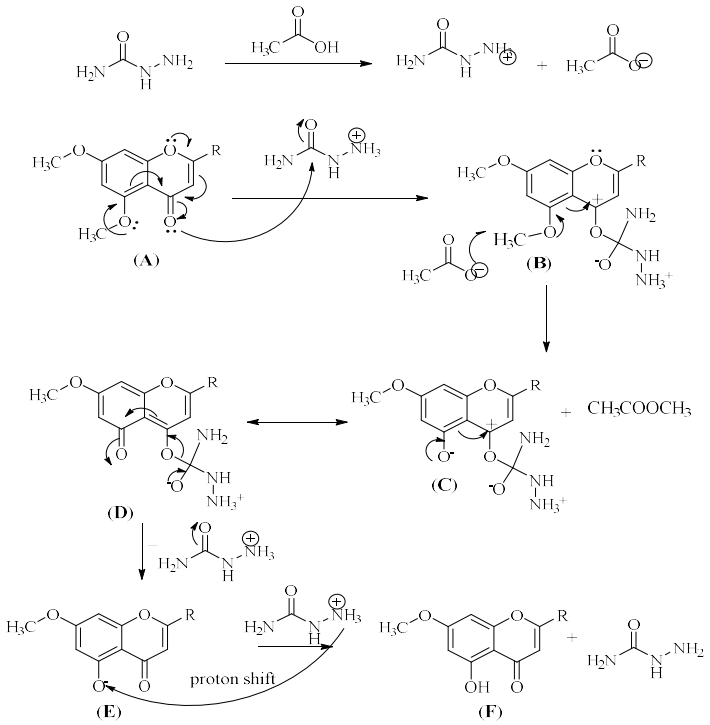
Table 1. Results of the reaction of the reagent semicarbazide-acetic acid system with various 5-O-methylated flavones, flavanones, aurones, chalcones, acetophenones.

Substrate (**1a-1j**)	Product (**2a-2j**)	Semicarbazide	
		Time	Yield
 **(1a)**	 **(2a)**	24 h	60
 **(1b)**	 **(2b)**	24 h	60
 **(1c)**	 **(2c)**	24 h	65
 **(1d)**	 **(2d)**	24 h	63
 **(1e)**	No reaction	>24h	--
 **(1f)**	No reaction	>24h	--
 **(1g)**	No reaction	>24h	--
 **(1h)**	No reaction	>24h	--
 **(1i)**	No reaction	>24h	--
 **(1j)**	No reaction	>24h	--
 **(1k)**			

Moreover, to establish the demethylation mechanism (Scheme 3) the reagent semicarbazide-acetic acid system is tested with various *O*-methylated chalcones, flavones, flavanones, aurones and acetophenones. Among the tested compounds only flavones yielded selective 5-*O*-demethylated products with 60-65% yields about 24 hrs at reflux temperatures (Table-1**)**. Chalcones, flavanones, aurones and acetophenones were not produced any demethylated product even maintained for longer hours (**1e-1k**). Moreover, the authors also tried the above reaction of flavone with different reagents

such as urea, thiourea, thiosemicarbazide and guanidine in presence of glacial acetic acid at reflux temperature, but, these reagents were not found suitable for demethylated product.

Based on the above results we tried to optimize the conditions by screening the selectivity of semicarbazide-acetic acid system with different equivalence ratio of semicarbazide-methylated flavone (1.0/1.0, 2.0/1.0, and 2.5/1.0) at reflux temperatures in acetic acid. Analyzing the results obtained clearly indicated that only 5-*O*-demethylated product was obtained even maintained for longer time for about 48 hrs. Thus the semicarbazide-acetic acid was the suitable system for the synthesis of selective 5-*O*-demethylated flavones. A tentative mechanistic scheme for the conversion of flavones to 5-*O*-demethylated flavones is as follows (Scheme 3).



Scheme 3. Schematic representation of formation of product

In the mechanism acetic acid proton may attach at semicarbazide NH_2 to form semicarbazide aceticacid complex. The oxygen of the carbonyl carbon of flavone (**A**) react with carbonyl carbon of the semicarbazide to form a intermediate (**B**) having positive charge at 4th position of flavone. Later, for neutralization of the positive charge on 4th position, the electrons may tend to donate from adjacent aromatic ring as shown in scheme and consequently the methyl and oxygen bond weakens to be attacked by the acetate ion on methoxy group and absorb the methyl group and forms the oxide anion 'C' and involve in resonance form 'D'. Finally the proton migrates from semicarbazonim ion to oxy anion of flavone (**E**) to afford 5-hydroxy flavone (**F**) as final product.

In this mechanism the double bond of the flavone plays very crucial role. It always push the polarizability of the carbonyl function of the flavone due to the +M effect of the oxygen of pyron ring and tendence to react with the another carbocation (of semicarbazide) to lead demethylation.

In case of flavanones there is no double bond in pyrone ring, so the polarizability of the ketone does not activated and therefore because of the weak polarizability it does not react with carbonyl carbon of semicarbazide. In a similar reason, the reaction does not take place in flavones and acetophenones of similar kind. In case of aurones and chalcones the -M effect dominates and the carbonyl carbon is not activated as the +M effect to give further reaction.

5. Conclusion

In summary, we have reported a novel and more easiest selective demethylation method for flavones by using semicarbazide, in glacial acetic acid at reflux temperatures for 24 hrs. The developed method was ecofriendly and specific for the 5-*O*-demethylation. The yields of the reactions are 60-65 %. Further, the method has broad scope for various 5-*O*-methylated heterocyclic and other flavones.

Acknowledgements

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Supporting Information

Supportinginformationaccompaniesthispaper on http://www.acgpubs.org/OC

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