ORIGINAL ARTICLE

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Org. Commun. 16:1 (2023) 46-53

organic communications

Synthesis and structure analysis of methyl 1-benzyl-5-(phenylamino)methyl)-1*H*-1,2,3-triazole-4-carboxylate

Guler Yagiz Erdemir and Aliye Altundas*

Department of Chemistry, Faculty of Science, Gazi University, 06560, Ankara, Türkiye

(Received February 21, 2023; Revised March 27, 2023; Accepted March 28, 2023)

Abstract: Azole motifs are commonly found in the pharmaceutical industry both as in commercial products and in the literature. In particular, the triazole motifs have many applications such as drug-like and gaining attention with the development of new anticorrosive compounds have made these motifs target molecules. In the literature, it is known that amino-triazole structures have chelating, antibacterial, enzyme inhibition, anti-TB properties, and excellent anticorrosion properties. In this study, the synthesis of novel 1-benzyl-5-(phenylamino)methyl-1,2,3-triazoles (**5a-g**) that could exhibit both drug-like interaction and corrosion inhibition properties was designed, synthesized and characterized. For this, **5a-g** were obtained in one step from reactions of methyl 1-benzyl-5-formyl-1*H*-1,2,3-triazole-4-carboxylate with anilines carrying different halogen atoms in the 2 and 4 positions. The structures of all the target molecules were fully elucidated by FT-IR, ^{1}H NMR, ^{13}C NMR.

Keywords: 1,2,3-Triazole; 5-formyl-1,2,3-triazole; regioselective synthesis; 5-(phenylamino)methyl-1,2,3-triazole

1. Introduction

Azole class scaffolds are remarkable molecules in many applications area.[1-5] Among them, the 1,2,3-triazole moiety is present in a broad variety of compounds such as pharmacological[8,9,10,11,14,15,18,19], material sciences[6], agriculture applications[7], corrosion inhibition[20] and in organic synthesis. [12,13,16,20] It is known that 1,2,3-triazole motifs demonstrate to immense activity in pharmacological applications, such as anticancer, anti-TB, XO enzyme inhibition, anti-inflammatory, ant plasmodial, and antibacterial agent.[6-19, 21-22] In particular, the triazole motifs have many applications such as drug-like and gaining attention with research for developing new anticorrosive compounds have made these motifs target molecules. Lots of methodologies are published for the synthesis of these motifs by day by. It is clearly evident in the literature that especially fully substituted 1,2,3-triazole structures containing formyl groups can easily be functionalized thanks to their high reactivity and fully substituted triazoles are drawn much attention due to using in numerous important organic molecule transformations.[4,12,23-27]

In the literature, it is known that amino-triazole hybrid structures have chelating, antibacterial, enzyme inhibition, anti-TB properties, pharmacological activities, and anticorrosive agents. Many studies have reported that amino methylene-triazole were synthesized for due to interacting with cellular fields such as potent BACE1 inhibitory activity, antibacterial activity, anticancer as seen Figure 1. [4, 24, 28-31]

Due to the potent pharmacological properties of the amino methylene-triazole ring, in this study is planned that it was synthesized triazoles containing the same ring of 5-(phenylamino) methyl- and 4-

* Corresponding author: E-Mail: aaltundas@gazi.edu.tr

The article was published by ACG Publications
http://www.acgpubs.org/journal/organic-communications © January-March 2023 EISSN:1307-6175
DOI: http://doi.org/10.25135/acg.oc.147.2302.2631
Available online: March 30, 2023

carboxylate groups. For this reason, we first formed a formyl group according to literature at the C5 position of the 1,2,3-triazole ring using the method we developed earlier[42]. Then, this formyl group reacted with appropriate aniline compounds to form 5-(phenylamino)methyl-1,2,3-triazole-4-carboxylate hybrid structures in one step.

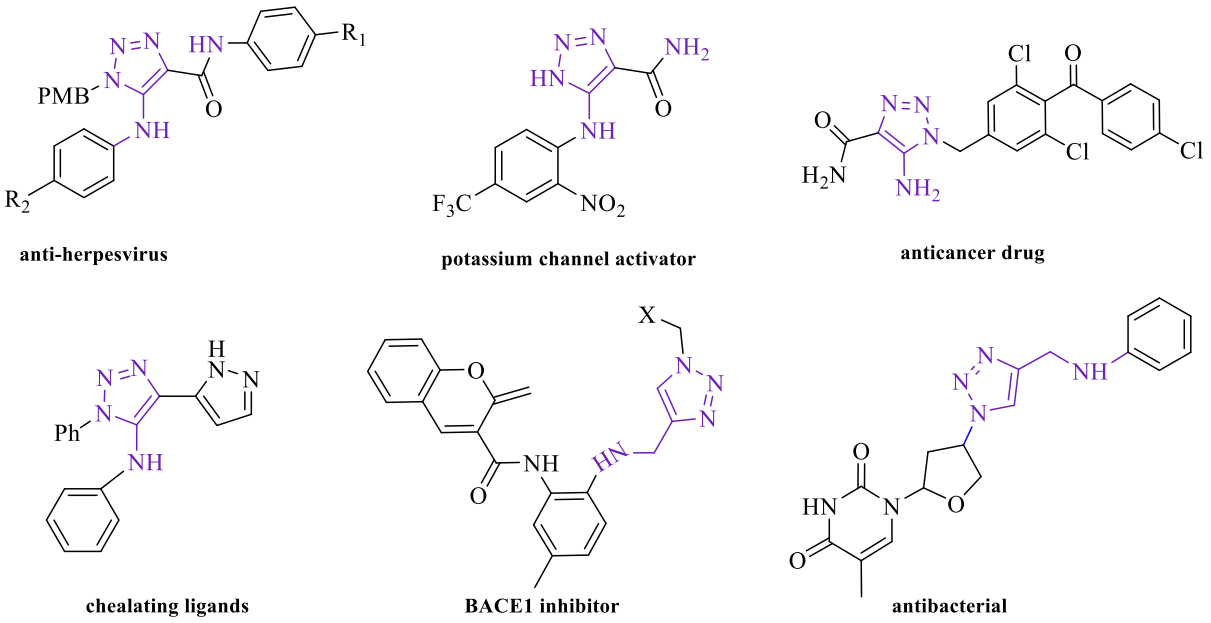


Figure 1. Some important amino methylene-triazole molecule structures

2. Experimental

2.1. Chemical Material and Instruments

Benzyl bromide, dimethyl acetylene dicarboxylate, lithium tri-*tert*-butoxy aluminum hydride (LTBA), aniline derivatives and all the solvents were purchased from Aldrich, Across and Merck. The tetrahydrofuran was dried in the presence of, sodium and benzophenone. For thin-layer chromatography (TLC), it was used Merck silica gel plates (SiO_2, 60 F254, 0.25 mm). The spots on the TLC were determined with UV (254 and 365 nm) light. Spectrum copies of all synthesized compounds are given in the supporting information.

The melting points of the final products were determined by the STUART (SMP-30) apparatus. Fourier-transform infrared (FTIR) spectra were screened on Perkin-Elmer Spectrum 100 FT-IR spectrophotometer as among 4000–500 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$-*d* on a Bruker Avance spectrometer 300 MHz and 75 MHz with. All the coupling constant values used were reported in Hertz. Chemical shifts were given in δ using the tetramethyl silane (TMS) standard and the splits were indicated as s, d, t and m, and these expressions are used instead of singlet, doublet, triplet and multiplet, respectively.

2.3. Chemistry

2.3.1. Synthesis of Dimethyl 1-benzyl-1H-1,2,3-triazole-4,5-dicarboxylate (3)

The dimethyl 1-benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylate molecule was synthesized by the method known in the literature.[19]

Compound ***3***[19]: Eluent: Hexane/EtOAc (6/4 v/v); yield: 98%; white solid; mp 48–49 °C. IR (ATR, cm^{-1}): ν 2958, 1723, 1491, 1435. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.25 (m, 5H, -C=C-H), 5.80 (s, 2H, $-CH_2-$), 3.95 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-OCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4 (C_{ester}), 158.8

(C_{ester}), 140.2 ($C_{arom.}$), 133.9 ($C_{arom.}$), 129.8 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.2 ($C_{arom.}$), 53.9 (C_{OMe}), 53.3 (C_{OMe}), 52.7 ($C_{methylene}$). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd. $C_{13}H_{13}N_3O_4Na^+$: 298. 0798, found 298. 0790.

*2.3.2. Regioselective Synthesis of Methyl 1-benzyl-5-formyl-1H-1,2,3-triazole-4-carboxylate (**4**)*

In order to reach the regioselective methyl 1-benzyl-5-formyl-1*H*-1,2,3-triazole-4-carboxylate motif, was used by the regioselective reduction method developed by our research group.[32] A solution of dimethyl 1-benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylate (1.0 equiv.) in anhydrous tetrahydrofuran at -10 °C was stirred for a while under argon gas. After the reaction mixture was allowed to cool to range from -10 to -5 °C temperature, reducing reagent (1.8 equiv., 1 M solution in THF) was drop wised with syringe into the reaction vessel. The reaction mixture was quenched with ice-water after 3h. Then, the mixture filtered from gooch-containing silica gel and washed with EtOAc. For the purification of the regioselective product (4) was carried out column chromatography from suitable solvent mixture (Scheme 1). Then, the obtained products were characterized by IR, ^{1}H, ^{13}C NMR spectroscopic techniques.[32]

*Compound **4***[32]: Eluent: Hexane/EtOAc (6/4 v/v); yield: 70%; white solid; mp 73–74 °C. IR (ATR, cm^{-1}): ν 3005, 2951, 2845, 1714, 1690, 1552, 1463. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H, H_{ald}), 7.32 (m, 5H, -C=C-H), 5.92 (s, 2H, -CH_2-), 4.03 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.9 (C_{formyl}), 160.6 (C_{ester}), 142.5 ($C_{arom.}$), 133.8 ($C_{arom.}$), 133.6 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.3 ($C_{arom.}$), 54.3 (C_{OMe}), 52.9 ($C_{methylene}$). HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd. $C_{12}H_{10}N_3O_3^-$: 244. 0728; found: 244. 0720.

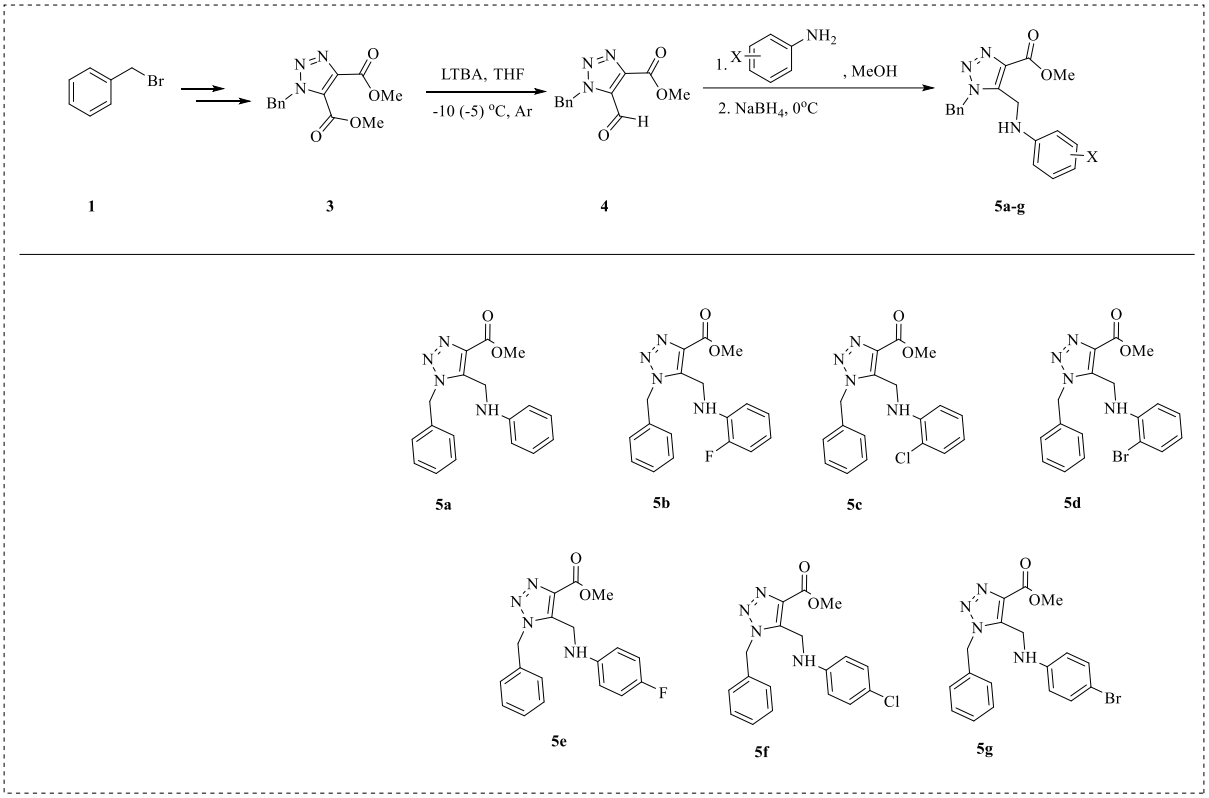
*2.3.3 General Synthesis Method of 5-(phenylamino)methyl-1,2,3-triazole derivatives (**5a-g**)*

Methyl 1-benzyl-5-formyl-1*H*-1,2,3-triazole-4-carboxylate (1.0 equiv.) was dissolved in MeOH (3 mL). And then in this solution was added dropwise substituted aniline derivatives (1.1 equiv.). The resulting mixture was stirred at room temperature overnight. After that, $NaBH_4$ (2.0 equiv.) was then added into the mixture in several portions in an ice-bath, and mixture was stirred at this temperature at 2-4h until reaction completing. After the reaction was complete, the mixture was neutralized with 2M HCl and extracted with DCM. The organic phases were dried with Na_2SO_4 and the solvent was removed under vacuum. Amino-triazole derivatives were purified by crystallization technique (Scheme 1). The obtained target products were characterized by IR, ^{1}H, ^{13}C NMR spectroscopic techniques.[16]

*Methyl 1-benzyl-5-((phenylamino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5a**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 70%, white solid, mp 127-128 °C. IR (ATR, cm^{-1}): ν 3320, 2918, 1715, 1601, 1521, 1495. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-6.53 (m, 10H); 5.68 (s, 2H, -CH_2-), 4.53 (s, 2H -CH_2-($_{amin}$)); 3.98 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1 (C_{ester}), 145.8 ($C_{arom.}$), 138.3 ($C_{arom.}$), 136.5 ($C_{arom.}$), 133.3 ($C_{arom.}$), 128.5 ($C_{arom.}$), 128.3 ($C_{arom.}$), 127.8 ($C_{arom.}$), 126.3 ($C_{arom.}$), 118.3 ($C_{arom.}$), 112.8 ($C_{arom.}$), 51.9 (C_{OMe}), 51.4 ($C_{methylene}$), 36.1($C_{methylene}$).

*Methyl 1-benzyl-5-(((2-fluorophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5b**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 64%, white solid, mp 122-124 °C. IR (ATR, cm^{-1}): ν 3375, 2955, 2921, 1713, 1619. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.14 (m, 5H), 6.99-6.58 (m, 4H), 5.7 (s, 2H, -CH_2-), 4.6 (bs, NH), 4.3 (s, 2H -CH_2-($_{amin}$)), 4.0 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (C_{ester}), 151.36 (d, *J* = 239.3 Hz) (C-$F_{arom.}$), 138.2 ($C_{arom.}$), 136.9 ($C_{arom.}$), 134.5 ($C_{arom.}$), 133.4 ($C_{arom.}$), 128.6 ($C_{arom.}$), 128.2 ($C_{arom.}$), 126.6 ($C_{arom.}$), 124.1 (d, *J* = 3.6 Hz) (C-$F_{arom.}$), 118.2 (d, *J* = 6.9 Hz) (C-$F_{arom.}$), 114.3 (d, *J* = 18.7 Hz) (C-$F_{arom.}$), 112.6 (d, *J* = 3.0 Hz) (C-$F_{arom.}$), 52.3 (C_{OMe}), 51.7 ($C_{methylene}$), 35.9 ($C_{methylene}$).

Synthesis of methyl 1-benzyl-5-(phenylamino)methyl)-1*H*-1,2,3-triazole-4-carboxylate



Scheme 1. Synthesized of 1-benzyl-5-amino methylene-1,2,3-triazoles

*Methyl 1-benzyl-5-(((2-chlorophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5c**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 65%, white solid, mp 118-119 °C. IR (ATR, cm^{-1}): ν 3379, 2952, 2922, 1712, 1598. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.05 (m, 6H), 6.7-6.6 (m, 3H) 5.7 (s, 2H, -CH_2-), 4.6 (s, 2H, -CH_2-($_{amin}$)), 4.0 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (C_{ester}), 142.4 ($C_{arom.}$), 138.5 ($C_{arom.}$), 137.5 ($C_{arom.}$), 133.8 ($C_{arom.}$), 129.4 ($C_{arom.}$), 129.3 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.0 ($C_{arom.}$), 127.2 ($C_{arom.}$), 119.9 ($C_{arom.}$), 119.1 ($C_{arom.}$), 111.8 ($C_{arom.}$), 53.1 (C_{OMe}), 52.3 ($C_{methylene}$), 36.4 ($C_{methylene}$).

*Methyl 1-benzyl-5-(((2-bromophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5d**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 68%, white solid, mp 109-110 °C. IR (ATR, cm^{-1}): ν 3368, 2922, 2852, 1709, 1594. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.08 (m, 7H), 6.66-6.57 (m, 2H), 5.7 (s, 2H, -CH_2-($_{amin}$)), 4.6 (bs, 3H, -CH_2-($_{amin}$), NH), 4.0 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (C_{ester}), 143.4 ($C_{arom.}$), 138.4 ($C_{arom.}$), 137.6 ($C_{arom.}$), 133.8 ($C_{arom.}$), 132.7 ($C_{arom.}$), 129.3 ($C_{arom.}$), 128.8 ($C_{arom.}$), 128.7 ($C_{arom.}$), 127.2 ($C_{arom.}$), 119.6 ($C_{arom.}$), 111.9 ($C_{arom.}$), 110.4 ($C_{arom.}$), 53.1 (C_{OMe}), 52.3 ($C_{methylene}$), 36.5 ($C_{methylene}$).

*Methyl 1-benzyl-5-(((4-fluorophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5e**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 72%, white solid, mp 147-148 °C. IR (ATR, cm^{-1}): ν 3315, 2953, 1727, 1556, 1525, 1508, 1496. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.31 (m, 3H), 7.21-7.11 (m, 2H), 6.85 (t, *J* = 8.7 Hz, 2H), 6.45 (dd, *J* = 8.9, 4.3 Hz, 2H). 5.67 (s, 2H, -CH_2-); 4.48 (s, 2H -CH_2-($_{amin}$)); 3.97 (b, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (C_{ester}), 156.7 (d, *J* = 237.1 Hz) (C-$F_{arom.}$), 143.0 ($C_{arom.}$), 139.1 ($C_{arom.}$), 137.4 ($C_{arom.}$), 134.1 ($C_{arom.}$), 129.2 ($C_{arom.}$), 128.8 ($C_{arom.}$), 127.2 ($C_{arom.}$), 115.8 (d, *J* = 22.5 Hz) (C-$F_{arom.}$), 114.9 (d, *J* = 7.4 Hz) (C-$F_{arom.}$), 52.8 (C_{OMe}), 52.3 ($C_{methylene}$), 37.6 ($C_{methylene}$).

*Methyl 1-benzyl-5-(((4-chlorophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5f**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 66%, white solid, mp 124-125 °C. IR (ATR, cm^{-1}): ν 3298, 2951, 1716, 1598, 1584,1492. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.13 (m, 5H), 7.09 (d,

J = 8.9 Hz, 2H), 6.43 (d, *J* = 8.9 Hz, 2H), 5.7 (s, 2H, -CH_2-), 4.5 (s, 2H, -CH_2-($_{amin}$)), 4.07 (bs, NH), 4.0 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (C_{ester}), 145.2 ($C_{arom.}$), 138.8 ($C_{arom.}$), 137.4 ($C_{arom.}$), 134.0 ($C_{arom.}$), 129.2 ($C_{arom.}$), 129.1 ($C_{arom.}$), 128.8 ($C_{arom.}$), 127.1 ($C_{arom.}$), 123.7 ($C_{arom.}$), 114.7 ($C_{arom.}$), 52.8 (C_{OMe}), 52.3 ($C_{methylene}$), 36.9 ($C_{methylene}$).

*Methyl 1-benzyl-5-(((4-bromophenyl)amino)methyl)-1H-1,2,3-triazole-4-carboxylate (**5g**)*: The product was purified by recrystallization from DCM/Hexane. Yield: 74%, white solid, mp 120-122 °C. IR (ATR, cm^{-1}): ν 3300, 2951, 1716, 1592, 1519, 1490. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 5.67 (s, 2H, -CH_2-), 4.49 (s, 2H -CH_2-($_{amin}$)), 3.97 (s, 3H, -OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0 (C_{ester}), 145.7 ($C_{arom.}$), 138.8 ($C_{arom.}$), 137.3 ($C_{arom.}$), 134.0 ($C_{arom.}$), 132.1 ($C_{arom.}$), 129.3 ($C_{arom.}$), 128.9 ($C_{arom.}$), 127.3 ($C_{arom.}$), 115.3 ($C_{arom.}$), 110.9 ($C_{arom.}$), 52.9 (C_{OMe}), 52.4 ($C_{methylene}$), 36.9 ($C_{methylene}$).

3. Results and Discussion

For the synthesis of *N*-benzyl-5-(phenylamino)methyl-1,2,3-triazoles **5a-g** compounds, methyl 1-benzyl-5-formyl-1*H*-1,2,3-triazole-4-carboxylate compound containing a regioselective formyl group was synthesized by the method we developed earlier with high yield and in one step. After that, **5a-g** were obtained from reactions of 4 with aniline molecules carrying different halogen atoms in the 2 and 4 positions. The intermediate methyl 1-benzyl-5-((phenylimino)methyl)-1*H*-1,2,3-triazole-4-carboxylate molecules were first synthesized. For this step, 5-(phenylamino)methyl-1,2,3-triazole with 4 and aniline derivatives mixed at room temperature in methanol at overnight. Then, a direct reduction step using $NaBH_4$ in an ice bath, was applied and target 5a-g molecules were synthesized in one step using a crystallization technique with yields up to 75%. The structures of all the target molecules were fully elucidated by FT-IR, ^{1}H NMR, ^{13}C NMR. The 5-(phenylamino)methyl-1,2,3-triazole motifs were investigated by reaction time and yield. Compared with **5b, 5c, 5d**, molecules **5e, 5f, 5g** were found to be higher yield and longer reaction time. It was seen that the yield of 5-(phenylamino)methyl-1,2,3-triazole reactions are significantly affected by steric factor of atomic diameter of halogens and at the 4-position (yield: 66%-74%) yields were higher than the 2-position (yield: 62%-68%) yields. Also, in the presence of the highest electronegative atom, fluor, was seen that the reaction time was minimized but the reaction yield was the worst.

In the FTIR spectrum of compound **4**, the -C=O stretch band belonging to the aldehyde group was observed to be intense at around 1700 cm^{-1}. Because of the conversion of compound **4** to compound **5**, this specific stretch band (-C=O) disappeared, and the -NH stretch band belonging to the amino group appeared at a wave number of around 3200 (Figure 2a, 2b).

In the ^{1}H NMR, the methyl 1-benzyl-5-formyl-1*H*-1,2,3-triazole-4-carboxylate compound obtained by regioselective reduction of compound **3**, one of the signals of methoxy groups was lost and the aldehyde proton appeared at around 10.5 ppm. In the target 5-(phenylamino)methyl-1,2,3-triazole compounds, it was confirmed that the target structures were synthesized that disappearing of the formyl proton at 10.5 ppm and resonating of the aliphatic -CH_2- group protons at 4.5 ppm (Figure 2a, 2c). Additionally, in ^{13}C NMR, the around 180 ppm -C=O peak belonging to the aldehyde group disappeared as a result with the reduction of the formyl group and the resulting methylene carbon (-CH_2-NH) resonated around 40 ppm (Figure 2a, 2d).

Briefly, we easily synthesized 5-(phenylamino)methyl-1,2,3-triazole hybrid structures thanks to this regioselective molecule including the aldehyde group and elucidated their structures. It is known in the literature that these triazole cores are important pharmacological and corrosion motifs and it predicts that these compounds will occur common in the literature thanks to its high application fields.

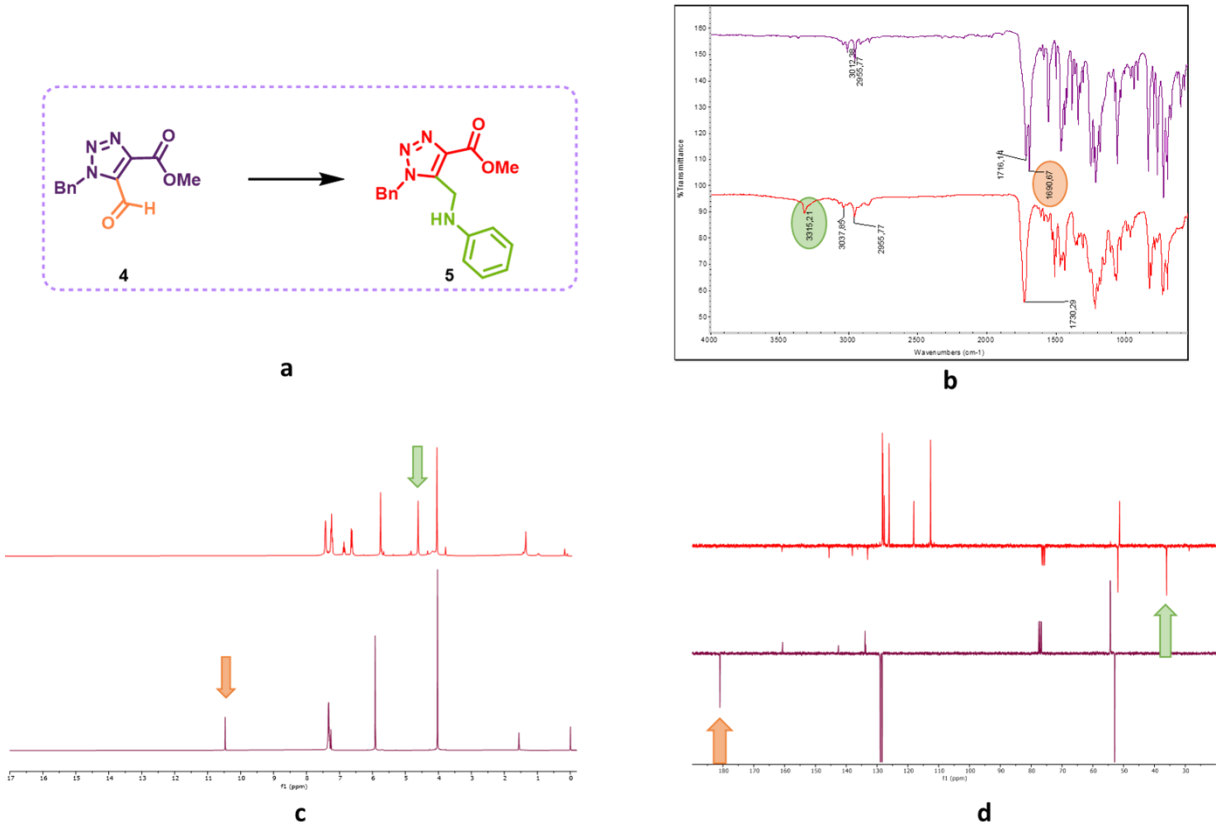


Figure 2. **a)** Transform scheme from compound **4** to compound **5a**; **b)** FTIR spectra of compound **4** and compound **5a**; **c)** ^{1}H NMR spectra of compound **4** and compound **5a**; **d)** ^{13}C-APT NMR spectra of compound **4** and compound **5a**.

4. Conclusion

Here, the synthesis of novel 1-benzyl-5-(phenylamino)methyl-1,2,3-triazoles **5a-g** that could exhibit both drug-like interaction and corrosion inhibition properties was designed, synthesized and characterized. Structures of **5a-g** were obtained from reactions of **4** with aniline molecules carrying different halogen atoms in the 2 and 4 positions. The structures of all the target molecules were fully elucidated by FT-IR, ^{1}H NMR, ^{13}C NMR. The reaction time and yield were investigated according to the substituents on aniline in the synthesized compounds. Compared with **5b, 5c, 5d**, molecules **5e, 5f, 5g** were found to be higher yield and longer reaction time.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

ORCID
Güler Yağız Erdemir: 0000-0003-2784-6391
Aliye Altundaş: 0000-0003-4616-4513

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