“One Flask” Synthesis to 3,5-Disubstituted 1,2,4-Triazoles from Aldehydes with Hydrazonoyl Hydrochlorides via 1,3-Dipolar Cycloaddition

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Abstract: A new “one-flask” synthesis of 3,5-disubstituted 1,2,4-triazoles has successfully been developed to synthesize a series of 3,5-disubstituted 1,2,4-triazoles. The transformation involves the 1,3-dipolar cycloaddition reaction of hydrazonoyl hydrochlorides with oxime intermediates prepared from aldehydes with hydroxylamine hydrochloride in the presence of excess amount of triethylamine. In this “one-flask” 1,3-dipolar reaction, hydrazonoyl hydrochlorides was concerned as the masked 1,3-dipole nitrilimine under basic condition. Furthermore, this newly developed methodology can be applied to various aldehyde substrates including aliphatic, cyclic aliphatic, aromatic, and heterocyclic aldehydes.

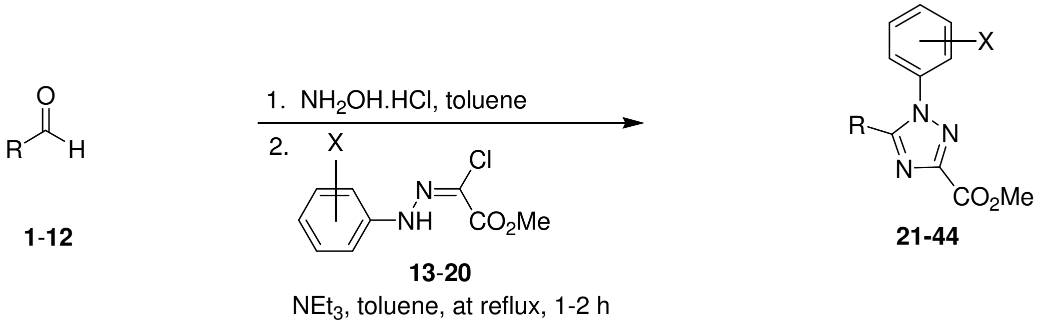
Introduction

Nitrilimine cycloadditions to ethylenic or ethylynic dipolarophiles are of great interest due to their potential application on the synthesis of variously bioactive 5-substituted-4,5-dihydrpyrazole heterocyclic derivatives.[1] Triazoles are also an important class of heterocyclic compounds, which is responsible for the biological activity of many pharmaceutically active compounds showing the antifungal,[2,3] antimicrobial,[4] antiviral,[5] anti-inflammatory,[6] anti-asthmatic,[7] antiproliferative,[8,9] hypotonic activities,[10] antibacterial, antifungal and antihelmintic activities.[11] More recently, triazole-based agonists or antagonists targeting different receptors were described,[12,13] especially molecules based on the 3,4,5-trisubstituted 1,2,4-triazole scaffold.[14–18] Herein, we provided an efficient methodology for the conversion of a series of aldehydes to 3,5-disubstituted 1,2,4-triazoles by use of hydrazonoyl hydrochlorides and hydroxylamine hydrate in the presence of triethylamine as a catalyst through the 1,3-dipolar cycloaddition mechanism.

It is well known that in situ generation of nitrilimines from hydrazonoyl chlorides[19] occurs in homogeneous aqueous system by base treatment. Hydrazonoyl chlorides were thus considered as the precursor for niritimines in aqueous base catalytic 1,3-dipolar cycloaddition.[1b] On the other hand, aldehydes were effectively converted to their oxime derivatives by means of hydroxylamine hydrochloride and are widely applied in the organic sysnthesis.[20] Hydrazonoyl chlorides and aldehydes were accordingly concerned as the masked agents for niritimines and oximes, respectively. In this paper, we reported a new 1,3-dipolar cycloaddition reaction for the synthesis 3,5-disubstituted 1,2,4-triazoles by reacting aldehydes with hydrazonoyl hydrochlorides using hydroxylamine hydrochloride as a transferring agent and triethylamine as a base catalyst. The newly developed method can be applicable to aliphatic, cyclic aliphatic, aromatic and heterocyclic aldehyde substrates to provide products in moderate to excellent yields.

Result and Discussion

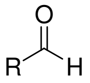
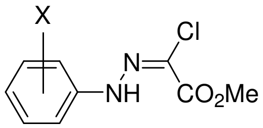
Aldehydes **1–12** are the commercially available materials. Various anilines were first converted to its corresponding diazonium salt by treatment with $NaNO_2$/HCl,[19] and then this intermediate was reacted with methyl 2-chloroacetoacetate to give hydrazonoyl chloride compounds **13–20**.[19] In the newly developed method, we treated a toluene solution of aldehydes **1–12** with 1.0 equiv of hydroxylamine hydrochloride with excess amount of triethylamine at room temperature for 0.5 h. When the aldehydes **1–12** were completely consumed and converted to the oxime intermediates,[20] then hydrazonoyl chloride **13–20** was added into the reaction mixture in the presence of excess amount of triethylamine and the solution was heated to reflux for 1–2 h. After the 1,3-dipolar cycloaddition reaction was completed, the filtration, concentration and purification with silica gel column chromatography were performed. The desired 3,5-disubstituted 1,2,4-triazole products **21–44** were isolated often in solid form (see Scheme 1).



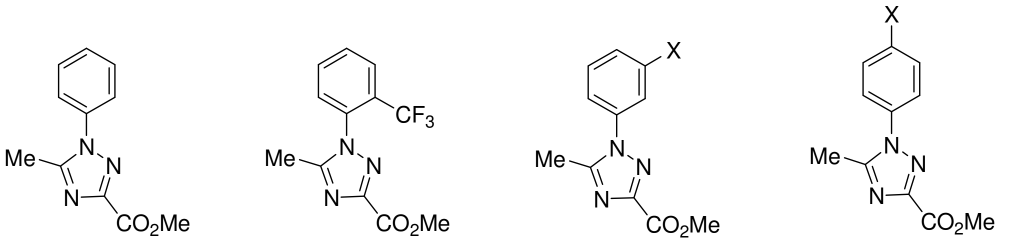
Scheme 1

To investigate the reactivity of hydrazonoyl hydrochlorides **13–20** with various substituents on the phenyl ring, acetaldehyde **1** was used as the model dipolarophile substrates. Acetaldehyde **1** was allowed to react with various aromatic hydrazonoyl hydrochlorides **13**–**20** bearing various substituents including F, Cl, Br, CF_3, and OMe at *ortho* or *meta* or *para* position to the nitrilimine group. The 1,3-dipolar cycloaddition smoothly proceeded to give the corresponding 3,5-disubstituted 1,2,4-triazole products **21**–**28** in good yields (53–91%, see the entries 1–8 in Table 1 and Chart 1). For compound **26** possessing the electron-donating *p*-methoxyl functionality in nitrilimine, the unreacted starting material was recovered from the reaction mixture as well as the less satisfactory result (53%, see the entry 6 of Table 1). Compounds **21**–**28** were fully characterized by spectroscopic methods. Served as an example, compound **21** possessed two characteristic peaks at 153.62 and 154.03 ppm, which represented the ^{13}C in triazole ring. The IR absorptions of **21** showed peaks at 1740 cm^{-1} for the stretching of the –C=O(OMe) carbonyl group. The assignment data of the corresponding product **21** was consistent with the literature data.[21] Results in Table 1 demonstrated that various substituents on the phenyl ring of the hydrazonoyl hydrochlorides were suitable for this newly developed method.

Table 1. Synthesis of 1,2,4-Triazole Derivatives Using Acetaldehyde (**1**) with Various Hydrazonoyl Hydrochlorides

Entry	Aldehydes 		Hydrazones 		1,2,4-Triazoles	Yield (%)
	R	No.	X	No.		
1	Methyl	**1**	H	**13**	**21**	88
2	Methyl	**1**	*o*-CF_3	**14**	**22**	87
3	Methyl	**1**	*m*-Br	**15**	**23**	86
4	Methyl	**1**	*m*-CF_3	**16**	**24**	85

5	Methyl	**1**	*p*-CF_3	**17**	**25**	87
6	Methyl	**1**	*p*-OMe	**18**	**26**	53
7	Methyl	**1**	*p*-Cl	**19**	**27**	86
8	Methyl	**1**	*p*-F	**20**	**28**	91



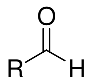
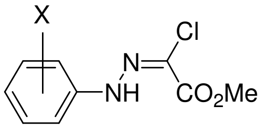
21 **22** **23**. X = Br **24**. X = CF_3 **25**. X = CF_3, **26.** X = OMe **27**. X = Cl, **28**. X = F

Chart 1

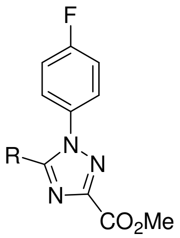
Fluorine-[22] and trifluoromethane-containing[23] compounds are well known to play an important role in bio- and agrochemical field. For example, replacement of hydrogen atoms by fluorine or trifluoromethane in pheromones has been shown to produce a variety of effects on the insect response. We thus turned our attention to synthesize a series of fluorine- or trifluoromethane-containing 3,5-disubstituted 1,2,4-triazole derivatives. *p*-Trifluoromethylphenylchlorohydrazone **17** and *p*-fluorophenylchlorohydrazone **20** were selected as the 1,3-dipole reactants for further evolution. On the other hand, due to the considerable substituent effect of the dipolarphile property on this 1,3-dipolar cycloaddition, we investigated *p*-fluorophenylchlorohydrazone **20** with variously substituted aldehydes **2–7** in the advanced priority model, including ethyl, *i*-propyl, *n*-butyl, cyclopropyl, cyclopentyl, and cyclohexyl substituted groups. When the normal 1,3-dipolar cycloaddition was performed, the corresponding fluorine-containing desired products **29–34** were successfully obtained in excellent yields (86–91%, see the entries 1–6 in Table 2 and Chart 2). The substituent effect of aliphatic and cyclic aliphatic aldehydes almost unchanged the reaction results.

This newly synthetic strategy was applied to *p*-fluorophenylchlorohydrazone **20** with the heterocyclic aldehydes **8**–**10**, involving furan-3-carbaldehyde **8**, thiophene-3-carbaldehyde **9**, and 1*H*-pyrrole-3-carbaldehyde **10**. The moderate yields were also achieved in 41–62% yields (see the entries 7–9 in Table 2 and Chart 2). When benzaldehyde **11** and 2-naphthaldehyde **12** were reacted with *p*-fluorophenylchlorohydrazone **20** under the same reaction condition, the less satisfactory yielding results were observed (33% and 28% yields, respectively, see the entries 10–11 in Table 2). Based on the simple FMO theory, nitrilimines are used as 1,3-dipoles. The dipoles LUMO and oxime hydrochlorides dipolarophile HOMO interaction has been suggested to be the interaction term in 1,3-dipolar cycloaddition.[19,20] Whatever, the electron rich dipolarophile of aromatic or heterocyclic aldehydes **8**–**12** would decrease both the frontier molecular orbital (FMO) energy barrier of the two reactants. Since, the dissatisfied isolated yields were provided in aromatic and heterocyclic reactants.

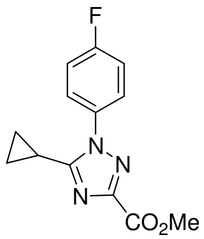
Table 2. The results of Synthesis of 1,2,4-Triazole derivatives from various of Aldehydes with Hydrazonoyl Hydrochlorides **17** or **20**.

Entry	Aldehydes 		Hydrazones 		1,2,4-Triazoles	Yield (%)
	R	No.	X	No.		
1	Ethyl	**2**	*p*-F	**20**	**29**	91
2	*i*-Propyl	**3**	*p*-F	**20**	**30**	90
3	*n*-Butyl	**4**	*p*-F	**20**	**31**	89
4	Cycloproyl	**5**	*p*-F	**20**	**32**	91

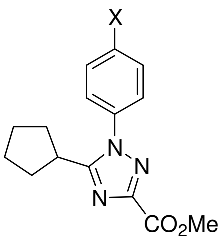
5	Cyclopentyl	**6**	*p*-F	**20**	**33**	88
6	Cyclohexyl	**7**	*p*-F	**20**	**34**	86
7	3-Furyl	**8**	*p*-F	**20**	**35**	62
8	3-Thienyl	**9**	*p*-F	**20**	**36**	57
9	2-pyrrolyl	**10**	*p*-F	**20**	**37**	41
10	Phenyl	**11**	*p*-F	**20**	**38**	33
11	2-Naphthyl	**12**	*p*-F	**20**	**39**	28
12	Cyclopentyl	**6**	*p*-CF_3	**17**	**40**	94
13	Cyclohexyl	**7**	*p*-CF_3	**17**	**41**	91
14	3-Furyl	**8**	*p*-CF_3	**17**	**42**	64
15	3-Thienyl	**9**	*p*-CF_3	**17**	**43**	62
16	2-pyrrolyl	**10**	*p*-CF_3	**17**	**44**	51



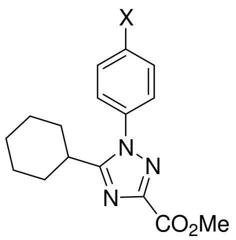
29. R = Et
30. R = *i*-Pr
31. R = *n*-Bu



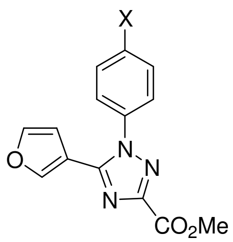
32



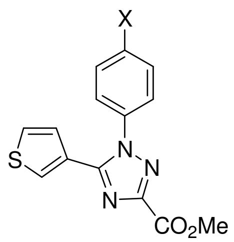
33. X = F
40. X = CF_3



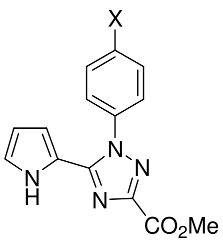
34. X = F
41. X = CF_3



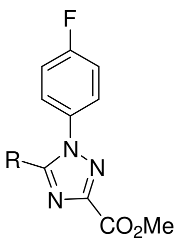
35. X = F
42. X = CF_3



36. X = F
43. X = CF_3



37. X = F
44. X = CF_3

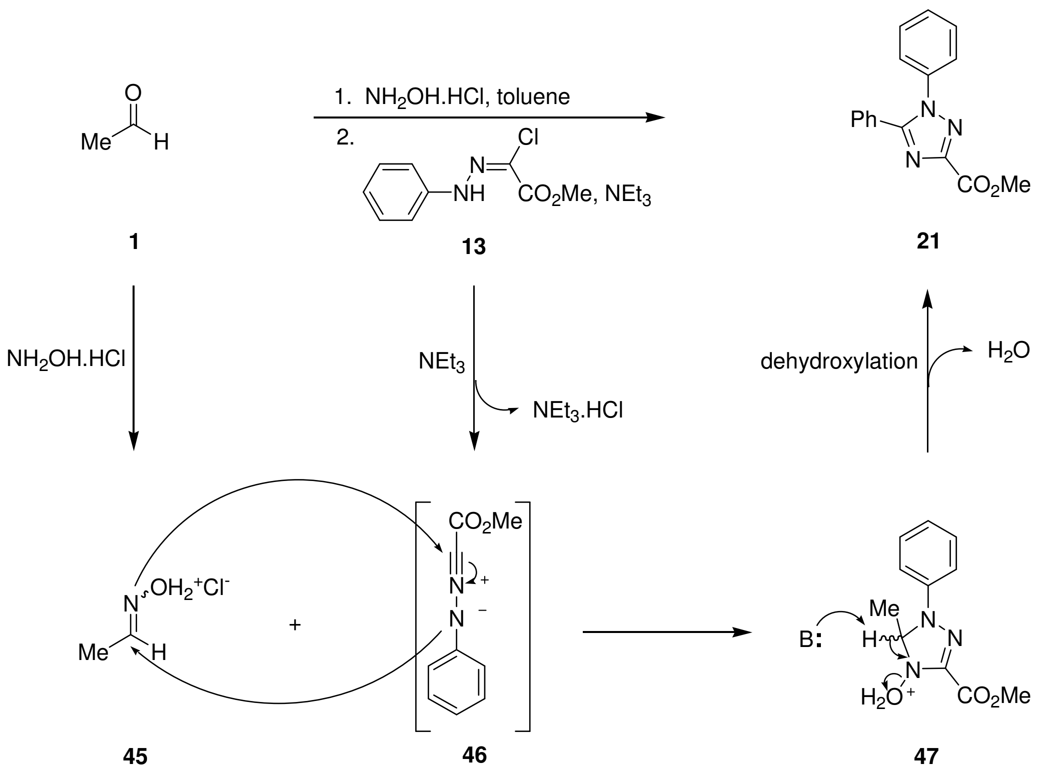


38. R = Ph
39. R = 2-Naphthyl

Chart 2

For the further demonstration of the substituent effect on the aldehyde dipolarophile reactants, we employed the above strategy to *p*-trifluoromethylphenylchlorohydrazone **17** with a series of cyclic aliphatic and heterocyclic aldehyde diplarophiles including cyclopentanecarboxaldehyde **6**, cyclohexanecarboxaldehyde **7**, furan-3-carbaldehyde **8**, thiophene-3-carbaldehyde **9**, 1*H*-pyrrole-3-carbaldehyde **10**. The same consistent tendency were achieved, the excellent isolated yields (91% and 94%) were obtained in cyclic aliphatic aldehydes **6** and 7, and the moderate to excellent yields were observed in heterocyclic aldehydes (51–64%, see the entry 14–16 of Table 2). The results also indicated the electron-rich aldehyde dipolarophiles, such as aromatic and heterocyclic aldehydes, were un-favored for the 1,3-dipolar cycloaddition reaction.

Consequently, we proposed the plausible mechanism for the effective 1,3-dipolar cycloaddition for the synthesis of 3,5-disubstituted 1,2,4-triazoles (see Scheme 2). Acetaldehyde **1** was reacted with 1.0 equivalent of hydroxylamine hydrochloride in toluene at reflux to generate oxime hydrochloride intermediate **45**. Treatment of hydrazonoyl hydrochloride **13** with excess amount of triethylamine resulted *in situ* generation of nitrilimine specie **46**. The requisite 1,3-dipolar cycloadduct dihydrotriazole **47** was formed by treating dipolarophile oxime **45** with 1,3-dipole nitrilimine **46**. When the subsequent dehydroxylation condensation was completed, the corresponding 3,5-disubstituted 1,2,4-triazole product **21** was obtained in good yield (88%, see Scheme 2).



Scheme 2

Conclusion

In conclusion, we have developed a new “one-flask” 1,3-dipolar cycloadditon method to prepare a series of 3,5-disubstituted 1,2,4-triazole compounds by reacting various aldehydes with hydrazonoyl hydrochlorides in the presence of hydroxylamine hydrochloride as a functionality transferring reagent and triethylamine as a basic catalyst. This new methodology can be widely applied to aliphatic, cyclic aliphatic, aromatic and heterocyclic aldehyde substrates and the corresponding 1,2,4-triazoles were obtained in moderate to excellent yields.

Experimental Section

All chemicals were reagent grade and used as purchased. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Mixtures of ethyl acetate and hexanes were used as eluants. Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene absorption at 1601 cm^{-1}. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz or 400 MHz) spectrometer by use of $CDCl_3$ as solvent. Carbon-13 NMR spectra were obtained on a Bruker (75 MHz or 100 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). ESI-MS spectra were obtained from an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer. Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Standard Procedure of One Flask Synthesis of 3,5-Disubstituted 1,2,4-Triazoles (19-44)

A solution of aldehyde derivatives (**1–12**, 1.0 mmol, 1.0 equiv), hydroxylamine hydrochloride (1.0 mmol, 1.0 equiv) were stirred at room temperature in toluene solution (6 mL) for 0.5 h. Then triethylamine (2.0 mmol, 2.0 equiv) and various of hydrazonoyl hydrochlorides (**13–20**, 1.0 mmol, 1.0 equiv) were added into the reaction mixture and heated to reflux within 1–2 h. When the reaction was completed, the reaction mixture was concentrated, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give the corresponding 3,5-disubstituted 1,2,4-Triazole products (**21**–**44**) in 28–91% yields.

1-Phenyl-3-methoxycarbonyl-5-methyl-1,2,4-triazole (21): yellow solid; mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3 H , CH_3), 3.90 (s, 3 H , CH_3), 7.35–7.46 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.12, 52.67, 124.79 (2 × CH), 129.49 (2 × CH), 129.51, 136.63, 153.62, 154.03, 160.27; IR (diffuse reflectance) 2955 (m), 1740 (s, C=O), 1597 (m), 1481 (m), 1431 (m), 1223 (s, C–O), 1145 (m), 1018 (m), 822 (m,), 772 (m) cm^{-1}; MS (ESI) *m/z*: 217 (M^+ + 1); Anal. Calcd for $C_{11}H_{11}N_3O_2$; C: 60.82; H: 5.10; N: 19.34, Found: C: 60.85; H: 5.07; N: 19.30.

1-(2-Trifluorophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (22): yellow solid; mp 83–84 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.27 (s, 3 H , CH_3), 3.91 (s, 3 H , CH_3), 7.33–7.37 (m, 1 H, ArH), 7.64–7.81 (m, 3 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.14, 52.70, 119.64, 125.09, 127.58, 127.66, 128.22, 129.78, 131.27, 133.24, 133.93, 153.98, 156.12, 160.10; IR (diffuse reflectance) 2955 (m), 1740 (s, C=O), 1605 (m), 1516 (m), 1458 (m), 1396 (m), 1319 (m), 1223 (m), 1138 (m), 779 (m) cm^{-1}; MS (ESI) *m/z*: 285 (M^+ + 1); Anal. Calcd for $C_{12}H_{10}F3N_3O_2$; C: 50.53; H: 3.53; N: 14.73, Found: C: 50.57; H: 3.50; N: 14.70.

1-(3-Bromophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (23): yellow solid; mp 119–120 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.54 (s, 3 H , CH_3), 3.95 (s, 3 H , CH_3), 7.35–7.38 (m, 2 H, ArH), 7.55–7.64 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.28, 52.84, 123.04, 123.20, 129.97, 130.75, 132.70, 137.66, 153.90, 154.14, 160.10; IR (diffuse reflectance) 3095 (m), 1740 (s, C=O), 1585 (m), 1470 (m), 1431 (m), 1219 (m), 1146 (m), 826 (m), 791 (m), 737 (m), 676 (m) cm^{-1}; MS (ESI) *m/z*: 295 (M^+ + 1); Anal. Calcd for $C_{11}H_{10}BrN_3O_2$; C: 44.62; H: 3.40; N: 14.19, Found: C: 44.58; H: 3.38; N: 14.21.

1-(3-Trifluorophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (24): yellow solid; mp 58–59 °C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.54 (s, 3 H , CH$_3$), 3.94 (s, 3 H , CH$_3$), 7.62–7.73 (m, 4 H, ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 13.23, 52.81, 120.39, 121.83, 121.89, 125.81, 126.25, 127.84, 130.32, 131.29, 131.95, 132.62, 133.28, 137.13, 154.06, 154.21, 160.02; IR (diffuse reflectance) 2955 (m), 1740 (s, C=O), 1600 (m), 1450 (m), 1389 (m), 1327 (m), 1065 (m), 899 (m), 806 (m), 694 (m) cm^{-1}; MS (ESI) *m/z*: 285 (M$^+$ + 1); Anal. Calcd for $C_{12}H_{10}F_3$ N_3O_2; C: 50.53; H: 3.53; N: 14.73, Found: C: 50.56; H: 3.50; N: 14.69.

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (25): light yellow solid; mp 117–118 °C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.54 (s, 3 H , CH$_3$), 3.91 (s, 3 H , CH$_3$), 7.59 (d, 2 H, *J* = 8.62 Hz, ArH), 7.72 (d, 2 H, *J* = 8.62 Hz, ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 13.34, 52.77, 102.62, 124.91, 126.04, 126.73, 126.80, 130.44, 131.13, 131.79, 132.45, 139.43, 154.06, 154.18, 160.00; IR (diffuse reflectance) 2959 (m), 1740 (s, C=O), 1616 (m), 1527 (m), 1477 (m), 1454 (m), 1015 (m), 860 (m), 741 (m) cm^{-1}; MS (ESI) *m/z*: 285 (M$^+$ + 1); Anal. Calcd for $C_{12}H_{10}F_3N_3O_2$; C: 50.53; H: 3.53; N: 14.73, Found: C: 50.55; H: 3.51; N: 14.75.

1-(4-Methoxyphenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (26): ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.49 (s, 3 H , CH$_3$), 3.84 (s, 3 H , CH$_3$), 3.98 (s, 3 H , CH$_3$), 6.96–7.00 (m, 2 H, ArH), 7.32–7.37 (m, 2 H, ArH); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 12.88, 52.58, 55.53, 114.49 (2 × CH), 126.24 (2 × CH), 129.40, 153.26, 154.10, 160.20, 160.26; IR (diffuse reflectance) 2928 (m), 1740 (s, C=O), 1516 (m), 1481 (m), 1400 (m), 1261 (m), 1219 (m), 1146 (m), 737 (m) cm^{-1}; MS (ESI) *m/z*: 247 (M$^+$ + 1); Anal. Calcd for $C_{13}H_{13}Cl$ N_4O_2; C: 53.34; H: 4.48; N: 19.14, Found: C: 53.35; H: 4.50; N: 19.13.

1-(4-Chlorophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (27): yellow solid; mp 118–119 °C; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.50 (s, 3 H , CH$_3$), 3.93 (s, 3 H ,

CH_3), 7.34–7.46 (m, 4 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.18, 52.77, 126.02 (2 × CH), 129.75 (2 × CH), 135.13, 135.58, 153.83, 154.08, 160.13; IR (diffuse reflectance) 2955 (m), 1740 (s, C=O), 1500 (m), 1477 (m), 1400 (m), 1223 (m), 1146 (s), 1096 (s), 1011 (s), 841 (m) cm^{-1}; MS (ESI) *m/z*: 251 (M^+ + 1); Anal. Calcd for $C_{11}H_{10}ClN_3O_2$; C: 52.50; H: 4.01; N: 16.70, Found: C: 52.48; H: 4.03; N: 16.74.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-methyl-1,2,4-triazole (28): yellow solid; mp 169–170 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3 H , CH_3), 3.92 (s, 3 H , CH_3), 7.10–7.18 (m, 2 H, ArH), 7.36–7.43 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.02, 52.73, 116.35, 116.82, 126.81, 126.99, 132.75, 153.71, 154.15, 160.17, 160.29, 165.28; IR (diffuse reflectance) 2963 (m), 1739 (s, C=O), 1516 (m), 1474 (m), 1427 (m), 1219 (m), 1150 (m), 845 (m), 810 (m), 671 (m) cm^{-1}; MS (ESI) *m/z*: 235 (M^+ + 1); Anal. Calcd for $C_{11}H_{10}F\ N_3O_2$; C: 56.17; H: 4.29; N: 17.86, Found: C: 56.14; H: 4.27; N: 17.87.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-ethyl-1,2,4-triazole (29): light yellow solid; mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, 3 H, *J* = 7.54 Hz, CH_3), 2.77 (q, 2 H, *J* = 7.54 Hz, CH_2), 3.93 (s, 3 H , CH_3), 7.12–7.21 (m, 2 H, ArH), 7.37–7.44 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.85, 19.97, 52.63, 116.27, 116.73, 127.11, 127.29, 132.59, 153.67, 159.02, 160.20, 165.25; IR (diffuse reflectance) 2986 (m), 1740 (s, C=O), 1520 (m), 1373 (m), 1204 (m), 1018 (m), 964 (m), 853 (m), 607 (m) cm^{-1}; MS (ESI) *m/z*: 249 (M^+ + 1); Anal. Calcd for $C_{12}H_{12}FN_3O_2$; C: 57.90; H: 4.87; N: 16.86, Found: C: 57.87; H: 4.89; N: 16.88.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-isopropyl-1,2,4-triazole (30): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (s, 3 H , CH_3), 1.31 (s, 3 H , CH_3), 2.94–3.15 (m, 1 H , CH), 3.95 (s, 3 H , CH_3), 7.13–7.21 (m, 2 H, ArH), 7.34–7.41 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.36 (2 × CH_3), 25.99, 52.79, 116.39, 116.85, 127.66, 127.83, 132.73, 153.90, 160.40, 163.14, 165.50; IR (diffuse reflectance) 2974 (m), 1740 (s, C=O), 1512 (m), 1481 (m), 1369 (m), 1227 (m), 1126 (m), 1015 (mw), 849 (m), 606 (m) cm^{-1}; MS (ESI) *m/z*: 263 (M^+ + 1); Anal. Calcd for $C_{13}H_{14}F N_3O_2$; C: 59.31; H: 5.29; N: 15.94, Found: C: 59.35; H: 5.32; N: 15.92.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-*n*-butyl-1,2,4-triazole (31): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.73 (t, 3 H, *J* = 8.62 Hz, CH_3), 1.10–1.29 (m, 2 H , CH_2), 1.54–1.69 (m, 2 H , CH_2), 2.63–2.71 (m, 2 H , CH_2), 3.89 (s, 3 H , CH_3), 7.05–7.17 (m, 2 H, ArH), 7.28–7.36 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.42, 22.12, 165.33; IR (diffuse reflectance) 2959 (m), 1740 (s, C=O), 1512 (m), 1223 (m), 1142 (m), 1015 (w), 849 (m), 613 (w) cm^{-1}; MS (ESI) *m/z*: 263 (M^+ + 1), 248 (11), 194 (32), 109 (100); Anal. Calcd for $C_{14}H_{16}F N_3O_2$; C: 60.64; H: 5.82; N: 15.15, Found: C: 60.62; H: 5.85; N: 15.11.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-cyclopropyl-1,2,4-triazole (32): yellow solid; mp 113–114 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.01–1.11 (m, 2 H , CH_2), 1.24–1.32 (m, 2 H , CH_2), 1.79–1.92 (m, 1 H , CH), 3.93 (s, 3 H , CH_3), 7.13–7.22 (m, 2 H, ArH), 7.49–7.59 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.44, 9.86 (2 × CH_2), 52.78, 116.28, 116.74, 127.09, 127.27, 132.82, 153.59, 159.72, 160.26, 165.23; IR (diffuse reflectance) 2954 (m), 1740 (s, C=O), 1601 (m), 1523 (m), 1203 (m), 1130 (m), 1022 (m), 957 (m), 517 (m) cm^{-1}; MS (ESI) *m/z*: 261 (M^+ + 1); Anal. Calcd for $C_{13}H_{12}F N_3O_2$; C: 59.77; H: 4.63; N: 16.08, Found: C: 59.75; H: 4.65; N: 16.04.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-cyclopentyl-1,2,4-triazole (33): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52–1.58 (m, 2 H , CH_2), 1.72–1.97 (m, 6 H , CH_2), 2.89–3.06 (m, 1 H, CH), 3.93 (s, 3 H , CH_3), 7.13–7.21 (m, 2 H, ArH), 7.35–7.42 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.62 (2 × CH_2), 32.81 (2 × CH_2), 36.20, 52.67, 116.27, 116.73, 127.60, 127.78, 132.81, 153.75, 160.38, 162.26, 165.38; IR (diffuse reflectance) 2958 (m), 1740 (s, C=O), 1512 (m), 1477 (m), 1412 (m), 1219 (m), 1134 (m), 1015 (m), 849 (m) cm^{-1}; MS (ESI) *m/z*: 288 (M^+ + 1); Anal. Calcd for

$C_{15}H_{16}FN_3O_2$; C: 62.27; H: 5.57; N: 14.52, Found: C: 62.30; H: 5.56; N: 14.49.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-cyclohexyl-1,2,4-triazole (34): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09–1.27 (m, 4 H , Cyclohexyl–H), 1.60–1.78 (m, 6 H , Cyclohexyl–H), 2.60–2.75 (m, 1 H , Cyclohexyl–H), 3.93 (s, 3 H , CH_3), 7.13–7.22 (m, 2 H, ArH), 7.32–7.41 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.17, 25.66 (2 × CH_2), 31.30 (2 × CH_2), 35.36, 52.63, 116.33, 116.79, 127.53, 127.71, 132.65, 153.79, 160.33 162.16, 165.37; IR (diffuse reflectance) 2940 (m), 1740 (s, C=O), 1605 (m), 1512 (m), 1447 (m), 1412 (m), 1366 (m), 1018 (m), 737 (m) cm^{-1}; MS (ESI) *m/z*: 303 (M^+ + 1); Anal. Calcd for $C_{16}H_{18}FN_3O_2$; C: 63.35; H: 5.98; N: 13.85, Found: C: 63.38; H: 6.01; N: 13.84.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-(3-furyl)-1,2,4-triazole (35): yellow solid; mp 145–146 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.94 (s, 3 H , CH_3), 6.39 (s, 1 H , ArH), 7.12–7.20 (m, 2 H, ArH), 7.32–7.33 (m, 1 H, ArH), 7.37–7.44 (m, 2 H, ArH), 7.49 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.87, 109.34, 113.53, 116.60, 117.06, 128.25, 128.42, 133.13, 143.52, 143.75, 150.37, 154.38, 160.13, 160.81, 165.81; IR (diffuse reflectance) 2954 (m), 1740 (s, C=O), 1609 (m), 1520 (m), 1470 (m), 1408 (m), 1200 (m), 810 (m) cm^{-1}; MS (ESI) *m/z*: 287 (M^+ + 1); Anal. Calcd for $C_{14}H_{10}F\ N_3O_3$; C: 58.54; H: 3.51; N: 14.63, Found: C: 58.56; H: 3.48; N: 14.64.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-(3-thienyl)-1,2,4-triazole (36): yellow solid; mp 148–149 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.97 (s, 3 H , CH_3), 3.95 (s, 3 H , CH_3), 7.10–7.27 (m, 4 H, ArH), 7.36–7.43 (m, 2 H, ArH), 7.48 (dd, 1 H, *J* = 1.23 Hz, *J* = 2.92 Hz ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.99, 116.60, 117.06, 126.66, 127.20, 128.11, 128.30 (2 × CH), 133.49, 152.07, 154.17, 160.26, 160.68, 165.68; IR (diffuse reflectance) 2954 (m), 1740 (s, C=O), 1566 (m), 1512 (s), 1474 (m), 1223 (m), 849 (m), 806 (m), 733 (m), 617 (m) cm^{-1}; MS (ESI) *m/z*: 303 (M^+ + 1); Anal.

Calcd for $C_{14}H_{10}F\ N_3O_2S$; C: 55.44; H: 3.32; N: 13.85, Found: C: 55.41; H: 3.29; N: 13.89.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-(2-pyrrolyl)-1,2,4-triazole (37): yellow solid; mp 226–227 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.98 (s, 3 H , CH_3), 5.78–5.81 (m, 1 H, ArH), 6.06–6.11 (m, 1 H, ArH), 6.89–6.93 (m, 1 H, ArH), 7.18–7.28 (m, 2 H, ArH), 7.46–7.52 (m, 2 H, ArH), 9.76 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.01, 110.42, 111.41, 116.63, 117.09, 118.11, 121.95, 128.67, 128.85, 133.40, 150.31, 153.69, 160.36, 160.90, 165.90; IR (diffuse reflectance) 3399 (br, NH), 1740 (s, C=O), 1593 (m), 1512 (m), 1481 (m), 1211 (m), 1180 (m), 814 (m), 737 (m) cm^{-1}; MS (ESI) *m/z*: 286 (M^+ + 1); Anal. Calcd for $C_{14}H_{11}FN_4O_2$; C: 58.74; H: 3.87; N: 19.57, Found: C: 58.76; H: 3.89; N: 19.60.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-phenyl-1,2,4-triazole (38): yellow solid; mp 166–167 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3 H , CH_3), 7.03–7.12 (m, 2 H, ArH), 7.25–7.48 (m, 7 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.90, 116.36, 116.83, 126.47, 127.43, 127.61, 128.68 (2 × CH), 129.03 (2 × CH), 130.74, 133.62, 154.26, 155.70, 160.23, 165.27; IR (diffuse reflectance) 2954 (m), 1740 (s, C=O), 1601 (m), 1513 (m), 1396 (m), 1223 (m), 1022 (m), 849 (m), 729 (m), 698 (m) cm^{-1}; MS (ESI) *m/z*: 297 (M^+ + 1); Anal. Calcd for $C_{16}H_{12}FN_3O_2$; C: 64.64; H: 4.07; N: 14.13, Found: C: 64.60; H: 4.10; N: 14.15.

1-(4-Fluorophenyl)-3-methoxycarbonyl-5-(2-naphthyl)-1,2,4-triazole (39): yellow solid; mp 139–140 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.03 (s, 3 H , CH_3), 7.06–7.14 (m, 2 H, ArH), 7.36–7.53 (m, 5 H, ArH), 7.73–7.81 (m, 3 H, ArH), 8.14 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.01, 116.44, 116.90, 123.68, 125.04, 127.04, 127.50, 127.68, 127.77, 127.93, 128.48, 128.70, 129.87, 132.65, 133.77, 133.89, 154.40, 155.81, 160.31, 165.33; IR (diffuse reflectance) 2955 (m), 1740 (s, C=O), 1454 (m), 1396 (m), 1229 (m), 1157 (m), 849 (m), 818 (m), 756 (m) cm^{-1}; MS (ESI) *m/z*: 347

(M^+ + 1); Anal. Calcd for $C_{20}H_{14}FN_3O_2$; C: 69.16; H: 4.06; N: 12.10, Found: C: 69.19; H: 4.17; N: 12.12.

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-cyclopentyl-1,2,4-triazole (40): Yellow solid; mp 75–76 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52–1.63 (m, 2 H , CH_2), 1.79–2.00 (m, 6 H, CH_2), 2.99–3.16 (m, 1 H, CH), 3.94 (s, 3 H , CH_3) 7.54–7.58 (d, 2 H, *J* = 8.52 Hz, ArH), 7.73–7.78 (d, 2 H, *J* = 8.52 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.69 (2 × CH_2), 33.06 (2 × CH_2), 36.36, 52.89, 115.24, 120.65, 125.92 (2 × CH), 126.73, 126.78, 130.73, 131.39, 132.05, 132.72, 139.56, 154.20, 160.31, 162.38; IR (diffuse reflectance) 2936 (m), 1739 (s, C=O), 1616 (m), 1327 (m), 1223 (m), 1065 (m), 1015 (m), 852 (s), 737 (m) cm^{-1}; MS (ESI) *m/z*: 339 (M^+ + 1); Anal. Calcd for $C_{16}H_{16}F_3N_3O_2$; C: 56.64; H: 4.75; N: 12.38, Found: C: 56.62; H: 4.74 N: 12.35

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-cyclohexyl-1,2,4-triazole (41): light yellow solid; mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22–1.33 (m, 4 H , Cyclohexyl–H), 1.67–1.82 (m, 6 H, Cyclohexyl–H), 2.68–2.83 (m, 1 H, Cyclohexyl–H), 3.99 (s, 3 H, CH_3), 7.54–7.59 (d, 2 H, *J* = 8.62 Hz, ArH), 7.78–7.82 (d, 2 H, *J* = 8.62 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.17, 25.7, 29.61, 31.48, 35.58, 52.83, 115.22, 120.65, 125.84, 126.78, 126.85, 130.76, 131.43, 132.08, 132.74, 139.50, 145.25, 160.26, 162.25; IR (diffuse reflectance) 2959 (m), 1739 (s, C=O), 1616 (m), 1483 (m), 1412 (m), 1227 (m), 1107 (m), 1015 (m), 852 (s) cm^{-1}; MS (ESI) *m/z*: 353 (M^+ + 1); Anal. Calcd for $C_{17}H_{18}F_3N_3O_2$; C: 57.79; H: 5.13; N: 11.89, Found: C: 58.77; H: 5.15; N: 11.88.

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-(3-furyl)-1,2,4-triazole (42): yellow solid; mp 155–156 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3 H , CH_3), 6.39 (s, 1 H , ArH), 7.39–7.41 (m, 1 H, ArH), 7.60–7.81 (m, 5 H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.13, 109.35, 113.28, 120.58, 122.13, 126.00, 126.47, 126.90, 126.96, 131.42, 132.08, 132.74, 133.40, 139.84, 143.88, 144.04, 144.31, 146.21, 150.21, 154.78, 160.09; IR (diffuse reflectance) 1743 (s, C=O), 1620 (m), 1535 (m), 1415 (m), 1327 (s), 1168 (m), 1123 (s), 1065(m), 845(s), 741(m) cm^{-1}; MS (ESI) *m/z*: 337 (M^+ + 1); Anal. Calcd for $C_{15}H_{10}F_3N_3O_3$; C: 53.42; H: 2.99; N: 12.46, Found: C: 53.46; H: 3.01; N: 12.45

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-(3-thienyl)-1,2,4-triazole (43): yellow solid; mp 85–86 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (s, 3 H , CH_3), 7.10 (dd, 1 H, *J* = 1.26 Hz, *J* = 4.24 Hz ArH), 7.30 (dd, 1 H, *J* = 2.98 Hz, *J* = 5.10 Hz ArH), 7.55–7.59 (m, 3 H, ArH), 7.72–7.76 (d, 2 H, *J* = 8.44 Hz, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 53.03, 114.44, 119.54, 120.62, 126.23 (2 × CH), 126.81, 126.88, 127.00, 127.09, 128.71, 131.73, 132.39, 140.18, 151.99, 154.57, 160.11; IR (diffuse reflectance) 3121 (m), 1740 (s, C=O), 1616 (m), 1566 (m), 1481 (m), 1443 (m), 1327 (s), 1227 (m), 1145 (s), 1065 (s) cm^{-1}; MS (ESI) *m/z*: 353 (M^+ + 1); Anal. Calcd for $C_{15}H_{10}F_3N_3O_2S$; C: 50.99; H: 2.85; N: 11.89, Found: C: 51.02; H: 2.84; N: 11.92

1-(4-Trifluorophenyl)-3-methoxycarbonyl-5-(2-pyrrolyl)-1,2,4-triazole (44): brown solid; mp 201–202 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.97 (s, 3 H , CH_3), 5.78–5.81 (m, 1 H, ArH), 6.06–6.11 (m, 1 H, ArH), 6.90–6.94 (m, 1 H, ArH), 7.65–7.69 (d, 2 H, *J* = 8.44 Hz, ArH), 7.78–7.82 (d, 2 H, *J* = 8.44 Hz, ArH), 9.92 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.99, 110.47, 111.74, 117.68, 120.65, 122.39, 126.08, 126.97 (2 × CH), 132.09, 132.75, 140.31, 150.17, 154.00, 160.18; IR (diffuse reflectance) 1740 (s, C=O), 1605 (m), 1493 (m), 1385 (m), 1327 (s), 1227 (m), 1126 (m), 1065 (m) cm^{-1}; MS (ESI) *m/z*: 336 (M^+ + 1); Anal. Calcd for $C_{15}H_{11}F_3N_4O_2$; C: 53.58; H: 3.30; N: 16.66, Found: C: 53.61; H: 3.31; N: 16.63.

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“One Flask” Synthesis to 3,5-Disubstituted 1,2,4-Triazoles from Aldehydes with Hydrazonoyl Hydrochlorides via 1,3-Dipolar Cycloaddition