ChemPubSoc Europe

DOI: 10.1002/ejoc.201600240

EurJOC European Journal of Organic Chemistry

Full Paper

Dipolar Cycloadditions

1,3-Dipolar Cycloaddition of Carbodiimides and Nitrilimines: Synthesis and Mechanistic Study of 5-Amino-1,2,4-triazoles

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Abstract: An effective 1,3-dipolar cycloaddition was developed for the synthesis of 5-amino-1,2,4-triazoles by reacting hydrazonoyl hydrochlorides (nitrilimines) with carbodiimides in the presence of triethylamine as a base. Both symmetric and asymmetric carbodiimides are compatible with this newly developed reaction; diphenyl carbodiimide is the one exception. Mechanistic studies indicate that alkyl and cycloalkyl moieties of the quaternary N^+–R on the 1,2,4-triazolic ring serve as potential leaving groups and can efficiently depart from the intermediate 4,5-dihydro-4-alkyl-5-imino-1,2,4-triazole.

Introduction

Polysubstituted 1,2,4-triazoles are an important class of heterocyclic compounds that display versatile biological activities.[1] In particular, the 5-amino-1,2,4-triazoles have drawn considerable attention due to their potential pharmaceutical applications in medicinal chemistry.[2–5] The typical synthetic methods for the preparation of 5-amino-1,2,4-triazoles involve thermal condensations between hydrazonoyl derivatives and cyanamide[6–9] or between *N*-cyanoimidates and mono-substituted hydrazines (see Figure 1).[10–13] However, both methods suffer from low yields, harsh reaction conditions, and requisite long reaction times. Although other approaches using 1,3,4-thiadiazol-2-amines[14] or aminoguanidine[15] as the starting materials have also been reported, these compounds are not commercially available and require multi-step preparations coupled with tedious purification procedures.[14,15] As a result, the development of a synthetic method for direct preparation of 5-amino-1,2,4-triazoles is particularly desirable.

Carbodiimides are valuable functional groups for synthetic chemistry, since they can be transferred to ureas,[16] imido carbonates,[17] imido amides,[18] guanidines,[19] oxazolidinone derivatives[20] as well as aromatic and non-aromatic heterocycles.[21] Conversely, hydrazonoyl hydrochlorides are attractive molecules because they serve as versatile precursors to the 1,3-dipolar cycloaddition reaction associated with generating five-membered heterocycles including pyrazoles,[22] pyrazole-fused compounds,[23] thiadiazoles,[24] 1,2,3-triazoles[25] and 1,2,4-triazoles.[26] However, 1,3-dipolar cycloaddition of carbodiimides with nitrilimines is rarely described in early reports.[27] In this work, we report an efficient and convenient synthetic route to 5-amino-1,2,4-triazoles and 1,2,4-triazoles via a 1,3-dipolar cycloaddition of hydrazonoyl hydrochlorides with both symmetric and asymmetric carbodiimides in the presence of triethylamine. Based on the mechanistic studies, the alkyl and cycloalkyl units of the quaternary N^+–R moieties on the 1,2,4-triazolic scaffold appear to function as leaving groups; such groups can depart from transiently formed 4,5-dihydro-4-alkyl-5-imino-1,2,4-triazole intermediate to generate 5-amino-1,2,4-triazole products. The isolation and characterization of triethyl *tert*-butylammonium chloride as the by-product provide strong evidence supporting the proposed mechanism. Further controlled experimental studies demonstrated that the activity and stability order of carbocation groups are: *tert*-butyl (3° carbocation) > cyclopentyl (2° carbocation) > isopropyl (2° carbocation) > cyclohexyl (2° carbocation) > ethyl (1° carbocation) >> phenyl (not detectable).

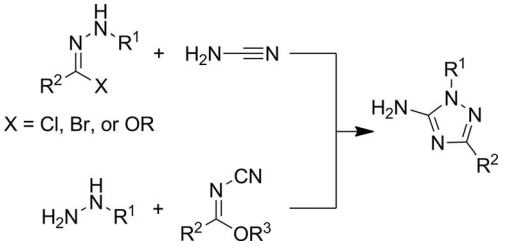

Figure 1. Two general synthetic pathways to 5-amino-1,2,4-triazoles.

Results and Discussion

A common feature of carbodiimides,[28] imidates,[29] and oximes[30] is that they all possess an imine functional group which can be used to construct heterocyclic aromatic compounds.[31] For instance, we have previously reported that the 1,3-dipolar

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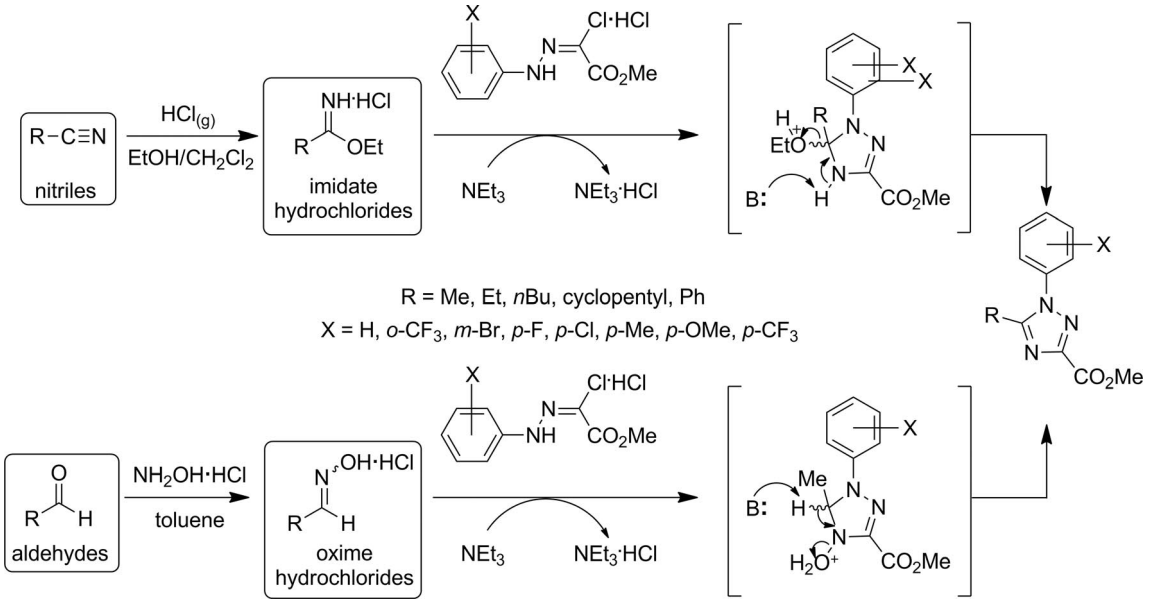
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600240.



Scheme 1. Our previously reported synthesis of 1,3,5-trisubstituted 1,2,4-triazoles via 1,3-dipolar cycloaddition reaction of nitrilimines with aldehydes, nitriles, imidate hydrochlorides, or oxime hydrochlorides.

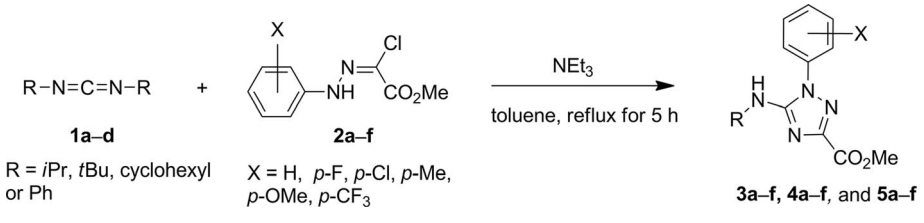
cycloaddition of nitrilimines with aldehydes, nitriles, imidate hydrochlorides, or oxime hydrochlorides can produce a series of 1,3,5-trisubstituted 1,2,4-triazoles (see Scheme 1).[26]

By employing the same reaction conditions shown in Scheme 1 and Scheme 2, we investigated the possibility of converting chemically similar carbodiimide compounds to their corresponding 1,2,4-triazoles (see Scheme 2). To start, we first extended this newly developed method to symmetric carbodiimides including diisopropylcarbodiimide **1a**, di-*tert*-butylcarbodiimide **1b**, dicyclohexylcarbodiimide **1c** and diphenylcarbodiimide **1d** (see Scheme 2).

The reaction was carried out by reacting carbodiimides **1a**–**d** with various hydrazonoyl chlorides **2a**–**f** bearing different *N*1 aryl substituents such as when X=H, *p*-F, *p*-Cl, *p*-Me, *p*-CF_3, or *p*-OMe (Table 1). The 1,3-dipolar cycloaddition went smoothly to give corresponding 5-amino-1,2,4-triazoles **3a**–**f**, **4a**–**f**, and **5a**–**f** in 60–96 % yields, except for when diphenylcarbodiimide **1d** was used as the dipolarophile where no desired product was observed (see Scheme 2 and Table 1). In the reaction of **1d** with **2e**, diphenylurea and *p*-chloroaniline were isolated as the hydrolysis and decomposition products of **1d** and **2e**, respectively.

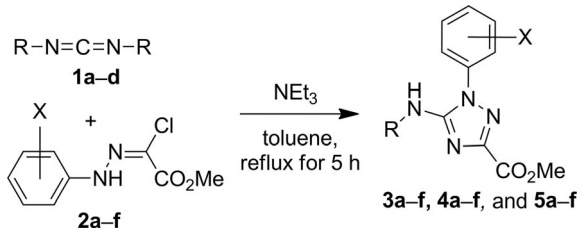
All 5-amino-1,2,4-triazoles **3a**–**f**, **4a**–**f**, and **5a**–**f** were fully characterized by spectroscopic methods including a single-crystal X-ray diffraction study (ORTEP) for compound **4c**. In ^{1}H NMR spectra of **4c**, resonances at δ = 1.42 ppm for *tert*-C(CH_3)$_3$ and 3.94 ppm for –OCH_3 were observed. In ^{13}C NMR spectra of compound **4c**, representative resonances at δ = 29.1 ppm for *tert*-C($^{13}CH_3$)$_3$, 52.6 ppm for *tert*-^{13}C(CH_3)$_3$, 152.6 and 154.0 ppm for 1,2,4-triazolic ring and δ = 160.7 ppm for the carbonyl carbon ^{13}CH=O were detected. The IR absorptions for compound **4c** showed peaks at 1730 cm^{-1} for stretching of the methyl ester group. The ORTEP drawing of compound **4c** is shown in Figure 2.

To reconfirm the lack of reactivity of diphenylcarbodiimide **1d**, we designed and synthesized a series of asymmetric carbodiimides,[32] including ethylphenylcarbodiimide **1e**, isopropylphenylcarbodiimide **1f**, *tert*-butylphenylcarbodiimide **1g**, cyclopentylphenylcarbodiimide **1h**, and cyclohexylphenylcarbodiimide **1i**, in order identify the substitution moiety at the *N*-position of carbodiimide (–N=C=N–). By adopting the same reaction conditions, hydrazonoyl hydrochloride **2e** was used as the model 1,3-dipolar reactant to react with asymmetric carbodiimides **1e**–**i** (Table 2). The 1,3-dipolar cycloaddition smoothly



Scheme 2. The new developed 1,3-dipolar cycloaddition for synthesis of 5-amino-1,2,4-triazoles using hydrazonoyl hydrochlorides with symmetric or asymmetric carbodiimides in the presence of triethylamine.

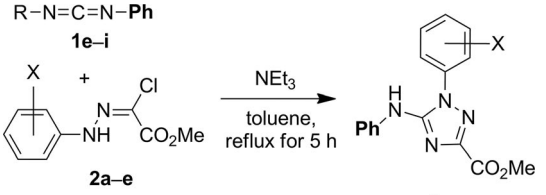
Table 1. Synthesis of 5-amino-1,2,4-triazole derivatives **3a–f**, **4a–f**, and **5a–f** using carbodiimides **1a–d** with various hydrazonoyl hydrochlorides **2a–f**.



Entry		R		X	Yield [%]	
1	**1a**	*i*Pr	**2a**	H	**3a**	85
2	**1a**	*i*Pr	**2b**	*p*-Me	**3b**	88
3	**1a**	*i*Pr	**2c**	*p*-CF_3	**3c**	91
4	**1a**	*i*Pr	**2d**	*p*-F	**3d**	92
5	**1a**	*i*Pr	**2e**	*p*-Cl	**3e**	96
6	**1a**	*i*Pr	**2f**	*p*-OMe	**3f**	91
7	**1b**	*t*Bu	**2a**	H	**4a**	89
8	**1b**	*t*Bu	**2b**	*p*-Me	**4b**	69
9	**1b**	*t*Bu	**2c**	*p*-CF_3	**4c**	93
10	**1b**	*t*Bu	**2d**	*p*-F	**4d**	78
11	**1b**	*t*Bu	**2e**	*p*-Cl	**4e**	72
12	**1b**	*t*Bu	**2f**	*p*-OMe	**4f**	60
13	**1c**	cyclohexyl	**2a**	H	**5a**	86
14	**1c**	cyclohexyl	**2b**	*p*-Me	**5b**	91
15	**1c**	cyclohexyl	**2c**	*p*-CF_3	**5c**	73
16	**1c**	cyclohexyl	**2d**	*p*-F	**5d**	96
17	**1c**	cyclohexyl	**2e**	*p*-Cl	**5e**	82
18	**1c**	cyclohexyl	**2f**	*p*-OMe	**5f**	91
19	**1d**	Ph	**2a**	H	0	

gave corresponding 5-amino-1,2,4-triazole **6e** in good yields (49–94 %, Table 2, Entries 1–5). Based on the result of control experiments, we found the order of activity for alkyl or cycloalkyl groups of asymmetric carbodiimides to be *tert*-butyl > cyclopentyl > isopropyl > cyclohexyl > ethyl >> phenyl. To realize the generality of this 1,3-dipolar cycloaddition reaction, we subjected the best dipolarophile *tert*-butyl-phenylcarbodiimide **1g** to hydrazonoyl chlorides **2a–d** bearing assorted *N*1 aryl groups with substitutions of X = H, *p*-F, *p*-Me, and *p*-CF_3 (Table 2). Accordingly, corresponding 5-amino-1,2,4-triazoles **6a–d** were smoothly obtained in good to excellent yields (32–76 %, Table 2, Entries 6–9).

Table 2. Synthesis of 5-amino-1,2,4-triazole derivatives using asymmetric carbodiimides **1e–i** with hydrazonoyl hydrochlorides **2a–e**.



R = *i*Pr, *t*Bu, cyclohexyl or Ph

X = H, *p*-F, *p*-Cl, *p*-Me, *p*-CF_3

Entry		R		X	Yield [%]	
1	**1e**	Et	**2e**	*p*-Cl	**6e**	49
2	**1f**	*i*Pr	**2e**	*p*-Cl	**6e**	61
3	**1g**	*t*Bu	**2e**	*p*-Cl	**6e**	94
4	**1h**	cyclopentyl	**2e**	*p*-Cl	**6e**	72
5	**1i**	cyclohexyl	**2e**	*p*-Cl	**6e**	50
6	**1g**	*t*Bu	**2a**	H	**6a**	41
7	**1g**	*t*Bu	**2b**	*p*-Me	**6b**	76
8	**1g**	*t*Bu	**2c**	*p*-CF_3	**6c**	32
9	**1g**	*t*Bu	**2d**	*p*-F	**6d**	63

To realize the different reactivity between dialkylcarbodiimides and diphenylcarbodiimide, we selected asymmetric carbodiimides **1e–i** as the model cases to explore and account for our proposed mechanism (see Scheme 3). At first, hydrazonoyl hydrochloride **2e** was converted to nitrilimine species **7** in the presence of an excess amount of triethylamine. Consequently, asymmetric carbodiimide dipolarophiles **1e–i** were treated with nitrilimine **7** to give cycloadduct dihydrotriazole intermediate **8**, the immediate 1,3-dipolar cycloaddition adduct. The less stable conformer **8**, a putatively kinetic product, was then converted

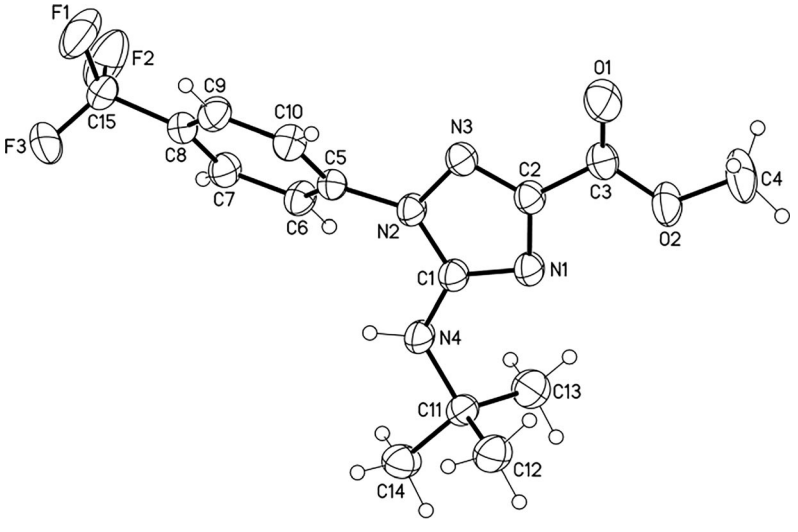
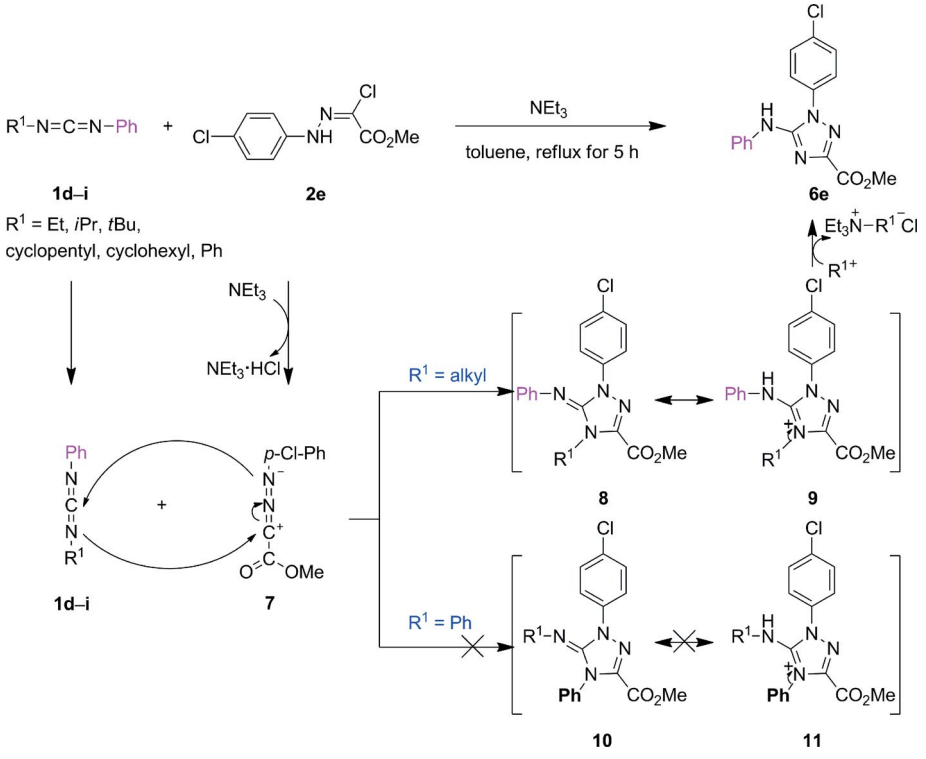


Figure 2. The ORTEP diagram of methyl 1-[4-trifloromethylphenyl]-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (**4c**).



Scheme 3. Predicted mechanism of asymmetric alkyl phenylcarbodiimide or symmetric diphenylcarbodiimide **1d** reacting with nitrilimines in a 1,3-dipolar cycloaddition.

to conformer **9**, which is more stable on the basis of resonance effects. We then came to realize that the alkyl or cycloalkyl unit of the quaternary N^+–R moiety of 4,5-dihydro-5-imino-1*H*-1,2,4-triazole intermediate **9** can serve as a leaving group thus forming alkyl or cycloalkyl carbocations by an E_1 reaction. Such carbocations, once formed, can be stabilized and trapped by triethylamine thus affording quaternary triethyl alkyl or cycloalkyl ammonium chloride salts. Notably, following routine work-up, triethyl *tert*-butylammonium chloride, a clearly relevant by-product, was isolated and identified by ^{1}H-NMR spectroscopy providing support for postulated mechanism (Figure 3). Alternatively, our experimental results are also consistent with reported carbocation stabilities dictating that the order of activity for asymmetric carbodiimides follows the trend that *tert*-butyl (3° carbocation) > cyclopentyl (2° carbocation) > isopropyl (2° carbocation) > cyclohexyl (2° carbocation) > ethyl (1° carbocation) >> phenyl cation. Finally, corresponding 5-amino-1,2,4-triazole **6a**–**e** products were obtained in 32–94 % yields (Table 2). However, cycloadduct dihydrotriazole intermediates **10** or **11** should be not efficiently formed in view of the noted instability of phenyl carbocations. As a result, 1,3-dipolar cycloadditions involving the Ph–N=C moiety of asymmetric alkyl or cycloalkylphenylcarbodiimides **1e**–**i** or symmetric diphenylcarbodiimide **1d** with nitrilimine species **7** are unproductive.

We speculate that solvent does not play a vital role in this reaction due to the fact that 1,3-dipolar cycloadditions involve a concerted process and the transition state is non-polar. To confirm this hypothesis, we carried out cycloaddition of di-*tert*-butylcarbodiimide **1b** with hydrazonoyl hydrochloride **2e**. Different solvents, including toluene, THF, CH_2Cl_2, MeOH, dioxane, and DMF were evaluated as reaction media. In aprotic solvents (toluene, THF, and CH_2Cl_2), 5-amino-1,2,4-triazole **4e** was obtained in good yields (72 %, 73 %, and 74 %, respectively, see Table 3, Entries 1–3). In protic solvents such as MeOH, **4e** was obtained in 68 % yield. Interestingly, the 1,3-dipolar cycloaddition failed to occur in polar solvents such as dioxane and DMF. Hence, our experimental results are in agreement with previously reported findings.[33]

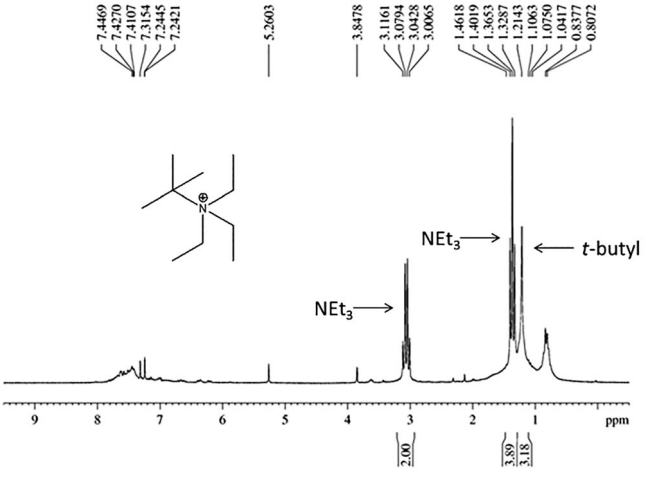
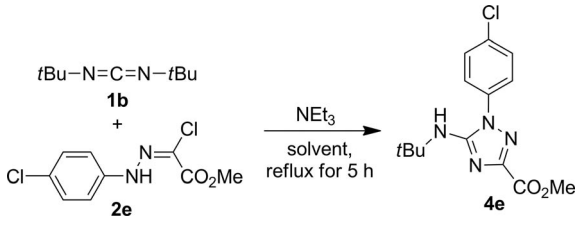


Figure 3. ^{1}H NMR spectrum of triethyl *tert*-butylammonium chloride.

Table 3. Study of solvent effect by using di-*tert*-butylcarbodiimide **1b** with hydrazonoyl hydrochlorides **2e**.



Entry	Reaction solvent	Reaction temp. [°C]	Yield [%] of **4e**
1	toluene	110–120	72
2	THF	60–75	73
3	CH_2Cl_2	45–55	74
4	MeOH	65–75	68
5	dioxane	100–110	–[a]
6	DMF	150–160	–[a]

[a] Non-detectable.

Conclusions

In conclusion, a new 1,3-dipolar cycloaddition for the effective synthesis of 5-amino-1,2,4-triazoles has been developed by treating symmetric or asymmetric carbodiimides with functionalized hydrazonoyl hydrochlorides in the presence of triethylamine as a base. Among the variously employed carbodimides, only diphenyl carbodiimide failed to serve as a substrate for the newly developed reaction. Further mechanistic studies suggest that the alkyl moieties of the carbodiimides function as suitable leaving groups able to readily depart from the 4,5-dihydro-5-imino-1,2,4-triazole intermediate thus forming the corresponding carbocations. Such carbocations can then be trapped by triethylamine to generate the quaternary triethyl alkylammonium chloride salt. This proposed mechanism is supported by the isolation and characterization of the ammonium salt. Further, the relative reactivity of asymmetric and symmetric carbodiimides was found to be consistent with the stability of subsequently formed carbocations; *tert*-butyl > cyclopentyl > isopropyl > cyclohexyl > ethyl >> phenyl.

Experimental Section

General: All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. ^{1}H NMR were recorded at 200, 400, or 500 MHz and ^{13}C NMR were recorded at 50, 100, or 125 MHz, respectively, in $CDCl_3$, CH_3OD, and [D_6]DMSO as solvents. The standard abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constant (*J*), whenever discernible, have been reported in Hz. Infrared spectra (IR) were recorded as neat solutions or solids; and mass spectra were recorded using electron impact or electrospray ionization techniques. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Flash column chromatography purification of compounds was carried out by gradient elution using hexanes in ethyl acetate (EA) unless otherwise stated. High-resolution mass spectra were obtained by means of a JEOL JMS-HX110 mass spectrometer.

Standard Procedure of Synthesis of 5-Amino-1,2,4-triazoles 3a–f, 4a–f, 5a–f, and 6a–e: A solution of symmetric carbodiimides (**1a**–**d**, 1.5 mmol, 1.5 equiv.) or asymmetric carbodiimides (**1e–i**, 1.5 mmol, 1.5 equiv.) was stirred at room temperature in toluene solution (10 mL) for 0.5 h. Then triethylamine (3.0 mmol, 3.0 equiv.) and various hydrazonoyl hydrochlorides (**2a**–**f**, 1.0 mmol, 1.0 equiv.) were added into the reaction mixture and heated to reflux within 5 h. When the reaction was complete, the reaction mixture was neutralized with aqueous 3 N HCl, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel to give corresponding 5-amino-1,2,4-triazoles **3a**–**f**, **4a**–**f**, **5a**–**f**, and **6a**–**e** in 53–96 % yields.

Methyl 1-Phenyl-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3a): Yellow solid; m.p. 150–154 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.34 (d, *J* = 6.9 Hz, 3 H, CH_3), 3.57 (sep, *J* = 6.9 Hz, 1 H), 3.96 (s, 3 H, OCH_3), 6.80–6.89 (m, 2 H, ArH), 7.10–7.18 (m, 3 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.61, 22.50, 29.65, 45.94, 52.91, 115.02 (2 × CH), 122.02, 129.02 (2 × CH), 136.51, 139.28, 159.48 ppm. IR (KBr): $\tilde{\nu}$ = 2924 (m), 1732 (s, C=O), 1600 (m), 1469 (m), 1319 (m), 1257 (s, C–O), 1124 (m), 750 (m), 690 (m) cm^{-1}. EIMS: *m/z* (%) = 260 (22) $[M]^+$, 229 (25), 218 (54), 212 (36), 197 (37), 118 (39), 105 (21), 91 (100), 77 (78), 65 (37). HRMS calcd. for $C_{13}H_{16}N_4O_2$, 260.1273, found 260.1270.

Methyl 1-*p*-Tolyl-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3b): Yellow solid; m.p. 185–189 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.33 (d, *J* = 6.8 Hz, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 3.59 (sep, *J* = 6.8 Hz, 1 H), 3.99 (s, 3 H, OCH_3), 6.76 (d, *J* = 8.3 Hz, 2 H, ArH), 6.93 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.57, 22.47, 29.64, 45.36, 52.81, 114.91 (2 × CH), 115.92, 129.93 (2 × CH), 131.29, 136.03, 136.94, 159.49 ppm. IR (KBr): $\tilde{\nu}$ = 2926 (m), 1730 (s, C=O), 1614 (m), 1469 (m), 1325 (m), 1255 (s, C–O), 1132 (m), 736 (m) cm^{-1}. EIMS: *m/z* (%) = 274 (27) $[M]^+$, 243 (25), 242 (22), 233 (40), 232 (100), 211 (47), 132 (29), 119 (22), 105 (41), 91(93). HRMS calcd. for $C_{14}H_{18}N_4O_2$, 274.1430, found 274.1436.

Methyl 1-[4-(Trifluoromethyl)phenyl]-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3c): Yellow solid; m.p. 164–168 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.35 (d, *J* = 6.8 Hz, 3 H, CH_3), 3.60 (sep, *J* = 6.8 Hz, 1 H), 3.99 (s, 3 H, OCH_3), 6.88 (d, *J* = 8.6 Hz, 2 H, ArH), 7.40 (d, *J* = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.74, 22.42, 29.70, 45.79, 53.24, 114.36, 115.07, 121.53, 123.54 (CF_3), 124.20 (CF_3), 124.85 (CF_3), 124.91 (CF_3), 126.47, 126.90, 137.68, 141.55, 159.14 ppm. IR (KBr): $\tilde{\nu}$ = 2926 (m), 1734 (s, C=O), 1616 (m), 1483 (m), 1315 (m), 1259 (s, C–O), 1126 (m), 738 (m), 592 (m) cm^{-1}. EIMS: *m/z* (%) = 328 (27) $[M]^+$, 297(48), 286(100), 265(66), 212(29), 186(48), 159(23), 145(82). HRMS calcd. for $C_{14}H_{15}F_3N_4O_2$, 328.1147, found 328.1142.

Methyl 1-(4-Fluorophenyl)-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3d): Yellow solid; m.p. 149–153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.34 (d, *J* = 7.0 Hz, 3 H, CH_3), 3.55 (sep, *J* = 7.0 Hz, 1 H), 3.96 (s, 3 H, OCH_3), 6.79–6.87 (m, 4 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.65, 22.47, 45.59, 52.99, 115.72, 115.90, 115.96, 116.30, 116.36, 135.52, 136.55, 157.37, 159.36 ppm. IR (KBr): $\tilde{\nu}$ = 3410 (m), 2924 (m), 1732 (s, C=O), 1546 (m), 1473 (m), 1323 (m), 1257 (s, C–O), 1122 (m), 744 (m) cm^{-1}. EIMS: *m/z* (%) = 278 (20) $[M]^+$, 247 (67), 236 (79), 230 (31), 215 (64), 162 (26), 136 (61), 123 (47), 109 (97), 95 (100), 83 (28). HRMS calcd. for $C_{13}H_{15}FN_4O_2$, 278.1179, found 278.1184.

Methyl 1-(4-Chlorophenyl)-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3e): Yellow solid; m.p. 198–202 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.8 Hz, 3 H, CH_3), 1.34 (d, J = 6.8 Hz, 3 H, CH_3), 3.55 (sep, J = 6.8 Hz, 1 H), 3.97 (s, 3 H, OCH_3), 6.75 (d, J = 9.2 Hz, 2 H, ArH), 7.11 (d, J = 9.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.70, 22.44, 45.63, 53.07, 115.87, 116.01 (2 × CH), 127.30, 129.16 (2 × CH), 136.85, 137.66, 159.23 ppm. IR (KBr): $\tilde{\nu}$ = 2953 (m), 1732 (s, C=O), 1595 (m), 1469 (m), 1323 (m), 1257 (s, C–O), 1130 (m), 821 (m), 678 (m) cm^{-1}. EIMS: *m/z* (%) = 294 (34) [M]$^+$, 280 (22), 263 (56), 252(100), 233 (24), 231 (63), 178 (23), 152 (48), 139 (35), 125 (77), 113 (25), 111 (76), 105 (20). HRMS calcd. for $C_{13}H_{15}ClN_4O_2$, 294.0884, found 294.0880.

Methyl 1-(4-Methoxyphenyl)-5-(isopropylamino)-1*H*-1,2,4-triazole-3-carboxylate (3f): Yellow solid; m.p. 163–167 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.8 Hz, 3 H, CH_3), 1.33 (d, J = 6.8 Hz, 3 H, CH_3), 3.57 (sep, J = 7.0 Hz, 1 H), 3.66 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.69 (d, J = 9.4 Hz, 2 H, ArH), 6.81 (d, J = 9.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.63, 22.49, 29.64, 45.40, 52.77, 55.26, 114.32 (2 × CH), 116.27 (2 × CH), 133.16, 135.84, 154.86, 159.49 ppm. IR (KBr): $\tilde{\nu}$ = 2924 (m), 1732 (s, C=O), 1462 (m), 1327 (m), 1265 (s, C–O), 1130 (m), 740 (s) cm^{-1}. EIMS: *m/z* (%) = 290 (32) [M]$^+$, 258 (22), 248 (100), 227 (34), 163 (25), 149 (34), 135 (51), 121 (62), 107 (92), 77 (23). HRMS calcd. for $C_{14}H_{18}N_4O_3$, 290.1379, found 290.1372.

Methyl 1-Phenyl-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4a): Yellow solid; m.p. 105–107 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *tert*-butyl), 3.89 (s, 3 H, OCH_3), 4.30 (s, 1 H, NH), 7.37–7.50 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.05 (3 × CH), 52.38, 52.80, 124.42 (2 × CH), 128.90, 129.86 (2 × CH), 136.02, 151.98, 154.00, 160.85 ppm. IR (KBr): $\tilde{\nu}$ = 3342 (m), 2964 (m), 1732 (s, C=O), 1568 (m), 1479 (m), 1315 (m), 1215 (s, C–O), 1145 (m), 761 (m), 696 (m) cm^{-1}. EIMS: *m/z* (%) = 274 (14) [M]$^+$, 218 (100), 91 (28), 77 (22). HRMS calcd. for $C_{14}H_{18}N_4O_2$, 274.1430, found 274.1437.

Methyl 1-*p*-Tolyl-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4b): Yellow solid; m.p. 130–132 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *tert*-butyl), 2.39 (s, CH_3), 3.93 (s, 3 H, OCH_3), 4.23 (s, 1 H, NH), 7.25–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.17, 29.16 (3 × CH), 52.45, 52.79, 124.50 (2 × CH), 130.47 (2 × CH), 133.46, 139.23, 154.15, 160.98 ppm. IR (KBr): $\tilde{\nu}$ = 3340 (m), 2924 (m), 1732 (s, C=O), 1568 (m), 1477 (m), 1369 (m), 1217 (s, C–O), 1145 (m), 821 (m), 729 (m) cm^{-1}. EIMS: *m/z* (%) = 288 (15) [M]$^+$, 232 (100), 105 (40), 91 (18). HRMS calcd. for $C_{15}H_{20}N_4O_2$, 288.1586, found 288.1588.

Methyl 1-[4-(Trifluoromethyl)phenyl]-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4c): Yellow solid; m.p. 148–150 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *tert*-butyl), 3.94 (s, 3 H, OCH_3), 4.23 (s, 1 H, NH), 7.65 (d, J = 8.0 Hz, 2 H, ArH), 7.77 (d, J = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.07 (3 × CH), 29.56, 52.63, 53.27, 124.20 (2 × CH), 127.16 (2 × CH), 131.44 (CF_3), 132.18 (CF_3), 132.77 (CF_3), 133.82 (CF_3), 139.25, 152.62, 154.00, 160.69 ppm. IR (KBr): $\tilde{\nu}$ = 3329 (m), 2964 (m), 1732 (s, C=O), 1571 (m), 1481 (m), 1369 (m), 1220 (s, C–O), 1130 (m), 846 (m), 727 (m) cm^{-1}. EIMS: *m/z* (%) = 342 (12) [M]$^+$, 286 (100), 226 (18), 159 (18), 57 (17). HRMS calcd. for $C_{15}H_{17}F_3N_4O_2$, 342.1304, found 342.1307.

Methyl 1-(4-Fluorophenyl)-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4d): Yellow solid; m.p. 1 40–142 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, *tert*-butyl), 3.88 (s, 3 H, OCH_3), 4.19 (s, 1 H, NH), 7.17 (t, J = 6.0 Hz, 2 H, ArH), 7.38–7.45 (m, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.02 (3 × CH), 52.49, 52.87, 116.68, 117.14, 126.66, 126.83, 131.98, 152.02, 154.13, 159.84, 160.74, 164.81 ppm. IR (KBr): $\tilde{\nu}$ = 3332 (m), 2964 (m), 1732 (s, C=O), 1556 (m), 1392 (m), 1219 (s, C–O), 1153 (m), 840 (m), 729 (m) cm^{-1}. EIMS: *m/z* (%) = 292 (13) [M]$^+$, 236 (100), 176 (24), 109 (57), 95 (22), 57 (21). HRMS calcd. for $C_{14}H_{17}N_4O_2$, 292.1336, found 292.1334.

Methyl 1-(4-Chlorophenyl)-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4e): Yellow solid; m.p. 150–154 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *tert*-butyl), 3.91 (s, 3 H, OCH_3), 4.21 (s,1 H, NH), 7.38–7.49 (m, 4 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.07, 29.54, 50.09, 52.52, 53.03, 125.74 (2 × CH), 130.13 (2 × CH), 134.69, 152.25, 154.03, 156.98, 160.76 ppm. IR (KBr): $\tilde{\nu}$ = 3361 (m), 2964 (m), 1732 (s, C=O), 1556 (m), 1392 (m), 1215 (s, C–O), 1141 (m), 842 (m), 738 (m) cm^{-1}. EIMS: *m/z* (%) = 308 (11) [M]$^+$, 254 (24), 252 (76), 125 (29). HRMS calcd. for $C_{14}H_{17}ClN_4O_2$, 308.1040, found 308.1037.

Methyl 1-(4-Methoxyphenyl)-5-(*tert*-butylamino)-1*H*-1,2,4-triazole-3-carboxylate (4f): Yellow solid; m.p. 126–128 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *tert*-butyl), 3.82 (s, CH_3), 3.92 (s, 3 H, OCH_3), 4.14 (s, 1 H, NH), 6.98 (d, J = 8.0 Hz, 2 H, ArH), 7.34 (d, J = 8.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.14 (3 × CH), 29.64, 52.49, 53.72, 55.55, 114.97 (2 × CH), 126.47 (2 × CH), 128.51, 151.73, 154.31, 159.92, 160.97 ppm. IR (KBr): $\tilde{\nu}$ = 3342 (m), 2960 (m), 1732 (s, C=O), 1568 (m), 1479 (m), 1392 (m), 1217 (s, C–O), 1147 (m), 835 (m), 731 (m) cm^{-1}. EIMS: *m/z* (%) = 304 (18) [M]$^+$, 248 (100), 135 (23), 121 (39). HRMS calcd. for $C_{15}H_{20}N_4O_3$, 304.1535, found 304.1531.

Methyl 1-Phenyl-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5a): Yellow solid; m.p. 148–152 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.76–1.78 (m, 11 H, cyclohexyl), 3.25–3.37 (m, 1 H, NH), 3.94 (s, 3 H, OCH_3), 6.80–6.86 (m, 3 H, ArH), 7.06–7.04 (m, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.56, 24.97, 26.29, 29.58, 29.74, 32.56, 52.83, 54.55, 114.98 (2 × CH), 115.83, 121.87, 128.82 (2 × CH), 136.36, 139.16, 159.56 ppm. IR (KBr): $\tilde{\nu}$ = 3441 (m), 2929 (m), 1732 (s, C=O), 1600 (m), 1469 (m), 1319 (m), 1257 (s, C–O), 1118 (m), 748 (m), 690 (m) cm^{-1}. EIMS: *m/z* (%) = 300 (6) [M]$^+$, 294 (29), 287 (28), 229 (79), 219 (97), 197 (86), 144 (44), 118 (54), 91 (54), 77 (100), 55 (83). HRMS calcd. for $C_{16}H_{20}N_4O_2$, 300.1586, found 300.1584.

Methyl 1-*p*-Tolyl-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5b): Yellow solid; m.p. 234–238 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89–1.73 (m, 11 H, cyclohexyl), 2.13 (s, 3 H, CH_3), 3.22–3.34 (m, 1 H, NH), 3.94 (s, 3 H, OCH_3), 6.73 (d, J = 8.6 Hz, 2 H, ArH), 6.91 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.53, 25.08, 26.37, 26.44, 29.85, 32.59, 52.81, 54.55, 115.02 (2 × CH), 115.62, 129.49 (2 × CH), 131.19, 136.01, 136.96, 159.71 ppm. IR (KBr): $\tilde{\nu}$ = 3286 (m), 2929 (m), 1730 (s, C=O), 1614 (m), 1469 (m), 1317 (m), 1259 (s, C–O), 1116 (m), 736 (m) cm^{-1}. EIMS: *m/z* (%) = 313 (11) [M]$^+$, 301 (22), 273 (20), 258 (23), 243 (45), 233 (64), 211 (57), 158 (31), 105 (46), 91 (100), 55 (44). HRMS calcd. for $C_{17}H_{22}N_4O_2$, 314.1743, found 314.1748.

Methyl 1-[4-(Trifluoromethyl)phenyl]-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5c): Yellow solid; m.p. 174–178 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82–1.84 (m, 11 H, cyclohexyl), 3.27–3.39 (m, 1 H, NH), 3.99 (s, 3 H, OCH_3), 6.85 (d, J = 8.6 Hz, 2 H, ArH), 7.38 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.96, 26.31 (2 × CH), 29.67, 30.03, 32.65, 53.20, 54.89, 114.43 (2 × CH), 114.71, 123.13 (CF_3), 123.63 (CF_3), 123.89 (CF_3), 124.01 (CF_3), 126.35, 126.37, 137.65, 141.56, 159.33 ppm. IR (KBr): $\tilde{\nu}$ = 3290 (m), 2929 (m), 1732 (s, C=O), 1614 (m), 1454 (m), 1317 (m), 1265 (s, C–O), 1114 (m), 740 (m) cm^{-1}. EIMS: *m/z* (%) = 368 (6) [M]$^+$, 297 (91), 287 (80), 265 (80), 212 (51), 186 (47), 145 (67), 83 (43), 55 (100). HRMS calcd. for $C_{17}H_{19}F_3N_4O_2$, 368.1460, found 368.1466.

Methyl 1-(4-Fluorophenyl)-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5d): Yellow solid; m.p. 201–205 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83–1.76 (m, 11 H, cyclohexyl), 3.22–3.34 (m, 1 H, NH), 3.93 (s, 3 H, OCH_3), 6.76–6.81 (m, 4 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.55, 26.31 (2 × CH), 29.62, 32.58, 52.94, 54.65, 115.43, 115.87, 116.25, 116.40, 135.45, 136.44, 155.79, 159.46, 160.58 ppm. IR (KBr): $\tilde{\nu}$ = 3446 (m), 2929 (m), 1732 (s, C=O), 1600 (m), 1454 (m), 1317 (m), 1265 (s, C–O), 1134 (m), 738 (m) cm^{-1}. EIMS: *m/z* (%) = 318 (4) $[M]^+$, 247 (53), 237 (55), 215 (45), 136 (44), 123 (44), 111 (42), 109 (58), 97 (51), 95 (77), 83 (69), 81, (46), 71 (52), 57 (78), 55 (100). HRMS calcd. for $C_{16}H_{19}FN_4O_2$, 318.1492, found 318.1495.

Methyl 1-(4-Chlorophenyl)-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5e): Brown solid; m.p. 193–197 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04–1.72 (m, 11 H, cyclohexyl), 3.09 (t, *J* = 12.0 Hz, 1 H, NH), 3.97 (s, 3 H, OCH_3), 6.73 (d, *J* = 9.0 Hz, 2 H, ArH), 7.09 (d, *J* = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.01, 26.33, 26.37, 29.94, 32.67, 53.07, 54.78, 115.12, 116.09 (2 × CH), 127.20, 129.97 (2 × CH), 136.83, 137.67, 159.43 ppm. IR (KBr): $\tilde{\nu}$ = 3290 (m), 2931 (m), 1732 (s, C=O), 1593 (m), 1465 (m), 1319 (m), 1246 (s, C–O), 1111 (m), 736 (m) cm^{-1}. EIMS: *m/z* (%) = 334 (13) $[M]^+$, 287 (26), 270 (25), 263 (79), 253 (52), 231 (87), 178 (29), 152 (83), 135 (68), 125 (58), 111 (63), 83 (42), 55 (100). HRMS calcd. for $C_{16}H_{19}ClN_4O_2$, 334.1197, found 334.1200.

Methyl 1-(4-Methoxyphenyl)-5-(cyclohexylamino)-1*H*-1,2,4-triazole-3-carboxylate (5f): Yellow solid; m.p. 120–122 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.77–1.70 (m, 11 H, cyclohexyl), 3.18–3.20 (m, 1 H, NH), 3.58 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.62 (d, *J* = 9.2 Hz, 2 H, ArH), 6.74 (d, *J* = 9.2 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.46, 29.50, 30.60, 32.47, 34.73, 52.65, 54.42, 55.04, 114.05 (2 × CH), 115.78, 116.29 (2 × CH), 132.99, 135.65, 154.63, 159.53 ppm. IR (KBr): $\tilde{\nu}$ = 3305 (m), 2929 (m), 1730 (s, C=O), 1514 (m), 1454 (m), 1317 (m), 1246 (s, C–O), 1130 (m), 736 (m) cm^{-1}. EIMS: *m/z* (%) = 330 (5) $[M]^+$, 248 (38), 227 (33), 135 (42), 121 (97), 107 (100), 55 (44). HRMS calcd. for $C_{17}H_{22}N_4O_3$, 330.1692, found 330.1696.

Methyl 1-Phenyl-5-(phenylamino)-1*H*-1,2,4-triazole-3-carboxylate (6a): Brown solid; m.p. 84–86 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 5 H, phenyl), 3.91 (s, 3 H, OCH_3), 7.65–7.76 (m, 5 H, ArH), 8.34 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.33, 29.66, 53.46, 114.49 (2 × CH), 119.70, 128.35, 128.60, 128.95, 129.45, 131.51, 132.13, 132.34, 133.75, 141.45, 160.17 ppm. IR (KBr): $\tilde{\nu}$ = 3275 (m), 2924 (m), 1728 (s, C=O), 1604 (m), 1435 (m), 1230 (s, C–O), 1026 (m), 713 (m) cm^{-1}. EIMS: *m/z* (%) = 294 (100) $[M]^+$, 293 (60), 185 (51), 183 (69), 93 (25). HRMS calcd. for $C_{16}H_{14}N_4O$, 294.1117, found 294.1114.

Methyl 1-*p*-Tolyl-5-(phenylamino)-1*H*-1,2,4-triazole-3-carboxylate (6b): Brown solid; m.p. 144–146 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.09–6.34 (m, 3 H, phenyl), 6.54–6.71 (m, 2 H, phenyl), 7.13–7.29 (m, 5 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.89, 112.56, 113.20, 113.85, 116.78, 121.71, 124.05, 124.09, 124.15, 126.64, 129.32, 129.74, 129.91, 131.33, 139.51, 140.58, 163.91 ppm. IR (KBr): $\tilde{\nu}$ = 3352 (m), 2920 (m), 1739 (s, C=O), 1604 (m), 1435 (m), 1257 (s, C–O), 1006 (m), 756 (m) cm^{-1}. EIMS: *m/z* (%) = 281 (77) [M^+ – 27], 270 (27), 230 (100), 214 (47), 206 (95), 152 (54), 135 (76), 91 (20), 77 (25). HRMS calcd. for $C_{17}H_{16}N_4O_2$, 308.1273, found 308.1276.

Methyl 1-[4-(Trifluoromethyl)phenyl]-5-(phenylamino)-1*H*-1,2,4-triazole-3-carboxylate (6c): Brown solid; m.p. 64–66 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, OCH_3), 6.95–7.12 (m, 4 H, phenyl), 7.45–7.54 (m, 5 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.94, 111.91, 113.03, 113.39, 114.10, 117.69, 121.61, 122.49, 124.40, 125.05, 126.37, 129.44, 132.22, 132.76, 138.64, 145.62, 160.81 ppm. IR (KBr): $\tilde{\nu}$ = 3344 (m), 2924 (m), 1716 (s, C=O), 1616 (m), 1435 (m), 1246 (s, C–O), 1064 (m), 748 (m) cm^{-1}. EIMS: *m/z* (%) = 362 (4) $[M]^+$, 230 (34), 206 (100), 145 (24), 135 (24), 118 (24), 93 (28), 77 (37). HRMS calcd. for $C_{17}H_{13}F_3N_4O_2$, 362.0991, found 362.0990.

Methyl 1-(4-Fluorophenyl)-5-(phenylamino)-1*H*-1,2,4-triazole-3-carboxylate (6d): Brown solid; m.p. 84–86 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.86 (s, 3 H, OCH_3), 6.06 (d, *J* = 6 Hz, 1 H, phenyl), 6.32–6.37 (m, 1 H, phenyl), 6.32–6.37 (m, 1 H, phenyl), 6.58–7.74 (m, 2 H, phenyl), 7.03–7.12 (m, 3 H, ArH), 7.32–7.39 (m, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.37, 112.34, 113.33, 115.93, 116.38, 124.27, 126.06, 126.23, 129.02, 131.68, 133.62, 137.42, 139.49, 158.09, 160.81, 162.96 ppm. IR (KBr): $\tilde{\nu}$ = 3332 (m), 2920 (m), 1732 (s, C=O), 1600 (m), 1435 (m), 1219 (s, C–O), 1014 (m), 752 (m) cm^{-1}. EIMS: *m/z* (%) = 285 (100, M^+ – 27), 224 (92), 194 (91), 133 (68), 105 (44), 95 (47), 91 (85), 77 (37). HRMS calcd. for $C_{16}H_{13}FN_4O_2$, 312.1023, found 312.1019.

Methyl 1-(4-Chlorophenyl)-5-(phenylamino)-1*H*-1,2,4-triazole-3-carboxylate (6e): Brown solid; m.p. 165–169 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, OCH_3), 6.23 (d, *J* = 8.0 Hz, 1 H, phenyl), 6.37 (d, *J* = 7.5 Hz, 1 H, phenyl), 6.63–6.73 (m, 2 H, phenyl), 7.32–7.36 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 53.39, 112.51, 113.62, 114.98, 117.12, 124.31, 124.53, 124.59, 129.18, 129.34, 130.32, 132.11, 132.74, 137.94, 141.67, 160.82 ppm. IR (KBr): $\tilde{\nu}$ = 3348 (m), 2927 (m), 1739 (s, C=O), 1589 (m), 1435 (m), 1265 (s, C–O), 1053 (m), 744 (m) cm^{-1}. EIMS: *m/z* (%) = 301 (33) [M^+ – 27], 206 (100), 194 (26), 91 (20). HRMS calcd. for $C_{16}H_{13}ClN_4O_2$, 328.0727, found 328.0729.

Acknowledgments

The authors are grateful to the China Medical University (CMU104-S-49) and the Tsuzuki Institute for Traditional Medicine for financial support. Prof. Cheng-Tung Lin and Ding-Yah Yang are thanked for kindly revising the manuscript.

Keywords: Cycloaddition · Regioselectivity · Nitrogen heterocycles · Carbodiimide · Nitrilimines

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Received: March 2, 2016
Published Online: April 13, 2016

