DOI: 10.1002/asia.200900320

An Efficient and Convenient Synthesis of Ethyl 1-(4-Methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate

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Abstract: The "click chemistry" of using organic azides and terminal alkynes is arguably the most efficient and straightforward route to the synthesis of 1,2,3-triazoles. In this paper, an alternative and direct access to ethyl 1-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate is described. Treatment of ethyl diazoacetate with 4-methoxyaniline derived aryl imines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene provided fully substituted 1,2,3-triazoles in good to high chemical yields. The base-mediated reaction tolerates various substituted phenyl imines as well as ethyl diazoacetate or the more bulky diazoacetamide. A reasonable mechanism is proposed that involves the addition of an imine nitrogen atom to the terminal nitrogen atom of the diazo compound, followed by aromatization to give the 1,2,3-triazole. The presence of the 4-carboxy group is advantageous as it can be easily transformed into other functional groups.

Keywords: aromaticity · cycloaddition · diazo compounds · heterocycles · triazoles

Introduction

1,2,3-Triazoles are interesting nitrogenous heterocycles because of their unique structure and chemical characteristics. These compounds have many applications in materials science, medicinal chemistry, and pharmacology.[1] Among methods for their synthesis, Hüisgen's 1,3-dipolar [3+2] cycloaddition of azides with alkynes is arguably the most popular and straightforward route to the five-membered heterocycles.[2] However, this methodology often requires an elevated temperature, and usually results in a mixture of 1,4- and 1,5-regioisomers. Meldal and co-workers and the group of Sharpless independently reported efficient routes to assemble the 1,4-disubstituted 1,2,3-triazoles by the cycloaddition of terminal alkynes to azides with Cu^{I} catalysis.[3] Selective access to the complementary 1,5-disubstituted triazoles was realized by using pentamethyl cyclopentadienyl ruthenium chloride [Cp*RuCl] complexes.[4] A welcome feature of the ruthenium-catalyzed cycloaddition reaction is its ability to catalyze internal alkynes with organic azides for the generation of 1,4,5-trisubstituted 1,2,3-triazoles. Previous methods that involved the introduction of a functional group to the existing 1,2,3-triazoles[5] or the use of activated acetylides or haloalkynes met with varying degrees of success.[6] However, several problems are commonly associated with these methods, such as slow reaction rates, high reaction temperature, the formation of regioisomers, and sometimes modest chemical yields. In addition, troublesome substrates, such as aryl azides and 1-aryl 5-substituted 1,2,3-triazoles, required the use of microwave irradiation at elevated temperatures to give the corresponding triazoles.[7] By examining the fully substituted 1,2,3-triazole structures, one can easily find that most of the substituents are either alkyl and aryl groups. This highlights the need for the synthesis of structurally diverse substituted 1,2,3-triazoles that can be used for further chemical transformation (for example, a 4- or 5-carbonyl group). A convenient direct synthesis of 1,4,5-trisubstituted 1,2,3-triazoles is lacking and alternative routes are yet to be developed.[8]

The organic diazo compound is a versatile reagent and can participate in diverse chemical transformations under various reaction conditions. These reactions involve aldol- or Mannich-type reactions,[9] cyclopropane ring formations,[10] X–H (X = O, N, C) bond insertion,[11] and unusual migration reactions.[12] The diazo compound could also react as a good 1,3-dipolar molecule by [3+2] cycloaddition to give heterocyclic compounds.[13] Herein, we report an alternative route for easy access to ethyl 1-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate using ethyl diazoace-

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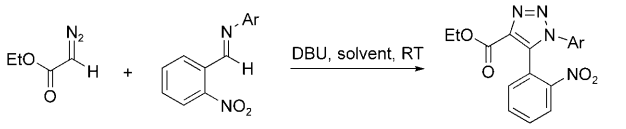
tate with 4-methoxyaniline derived imines under mild reaction conditions.

Results and Discussion

We first examined the reaction between ethyl diazoacetate (**1a**) and various imines in the presence of a base. An extensive screen of amine bases (e.g., 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,1,3,3-tetramethylguanidine (TMG), 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP)) and imines ($BocNH_2$, $OBnNH_2$ derived aryl imines; Boc = *tert*-butyloxycarbonyl) failed to give the 1,2,3-triazole nucleus. To our surprise, *N*-PMP (*N*-*p*-methoxyphenyl)imine **2a** and ethyl diazoacetate (**1a**) in CH_3CN and in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided an unexpected 1,4,5-trisubstituted 1,2,3-triazole **3aa** (Table 1). It was further observed that 3.0 equiv of

Table 1. Survey of *N*-substituents and solvents in DBU-promoted 1,2,3-triazole synthesis.[a]



1a **2a** **3aa**

Entry	Ar	Solvent	*t* [h]	Yield [%][b]
1	PMP	CH_3CN	1	76
2	PMP	none	4	34
3	PMP	MeOH	24	35
4	PMP	CH_3CH_2CN	4	60
5	PMP	DMF	1	47
6	PMP	CH_2Cl_2	4	55
7	PMP	THF	24	30
8	PMP	diethyl ether	24	20
9	PMP	toluene	24	25
10	PMP	1,4-dioxane	48	26
11	phenyl	CH_3CN	2	64
12	4-nitrophenyl	CH_3CN	2	54

[a] Reaction conditions: aryl imine (**2**; 1.2 equiv) was dissolved in the solvent indicated and ethyl diazoacetate (**1a**; 50 μL, 1.0 equiv) and base (3.0 equiv) were subsequently introduced. [b] Yield of isolated product.

DBU was essential to give 1,2,3-triazoles with a good chemical yield (Table 1, entry 1). To further improve the chemical yield, solvent effects were examined. When the reaction was carried out under neat conditions or in methanol, low chemical yields were obtained (Table 1, entries 2 and 3). Both the reactivity and chemical yields decreased when oxygenated solvents were used (Table 1, entries 7, 8, and 10). It was obvious that CH_3CN was the most suitable solvent for the reaction. Interestingly, the chemical yields decreased when (*E*)-*N*-(2-nitrobenzylidene)benzenamine and (*E*)-*N*-(2-nitrobenzylidene)-4-nitrobenzenamine were used (Table 1, entries 11 and 12).

To optimize the reaction conditions further, the effect of the substrate ratio was also examined (Table 2). The use of stoichiometric amounts of **1a** and **2a** resulted in 45% chemical yield (Table 2, entry 1). The chemical yield was significantly improved when 4.0 equiv of the electrophile **2a** was used (Table 2, entry 3). In contrast, the reactivity dropped and the chemical yields decreased when higher concentrations of **1a** were used (Table 2, entries 4–8). Decomposition of ethyl diazoacetate was observed under these reaction conditions. The optimum reaction conditions were realized for the direct assembly of fully substituted 1,2,3-triazoles by the reaction of **1a** and *N*-PMP aryl imines.

Table 2. Optimization of the [3+2] cycloaddition reaction.

Entry	**1a** [equiv]	**2a** [equiv]	*t* [h]	Yield (**3aa**) [%][a]
1	1.0	1.0	24	45
2	1.0	1.2	1	76
3	1.0	4.0	2	90
4	2.0	1.0	24	62
5	4.0	1.0	24	53
6	6.0	1.0	24	47
7	8.0	1.0	24	36
8	10.0	1.0	24	26

[a] Yield of isolated product.

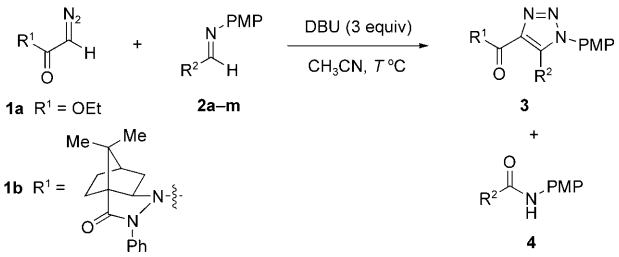
The scope of the reaction with a variety of *N*-PMP aryl imines was investigated (Table 3). Various substituted *N*-PMP imines **2a**–**m** reacted efficiently with **1a** to produce fully substituted 1,2,3-triazoles. The use of nonsubstituted and electron-withdrawing substituted aryl imines yielded the desired adduct in good to high chemical yields (Table 3, entries 1–6). However, for some of the substrates (Table 3, entries 2–4 and 6) the reaction proceeded with the isolation of the oxidized amides **4** in yields of 15–25%. The structure of the *N*-PMP derived amide compound **4** was confirmed by ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray analysis. The reactivity decreased when halogenated aryl imines were used, and reasonable to good chemical yields were obtained (Table 3, entries 7–9).

For electron-donating substituent aryl imines, the reaction temperature was raised to 50°C to give the triazoles in 67% and 64% chemical yields (Table 3, entries 10 and 11). Heterocyclic substituted *N*-PMP imines were also good substrates for the 1,2,3-triazole synthesis at 50°C, and high chemical yields were obtained (Table 3, entries 12 and 13). The structures of compound **3aa**, **3ab**, and **3al** were further confirmed by single-crystal X-ray analyses.[14] In addition to **1a**, camphor pyrazolidinone[15] derived α-acetamide **1b** is also effective in this reaction (Table 3, entries 14 and 15). This

Abstract in Chinese:

有機疊氮化合物與炔類的[3+2]環化加成反應是目前最直接有效製備 1,2,3-triazole 的方法，然而此反應條件必須加熱、或使用金屬催化劑，然如欲製備三取代 1,2,3-triazole 化合物，有其合成上的限制。我們在此報導利用重氮(diazo)化合物與亞胺(imine)分子為起始物，加入鹼試劑後即可一步反應得到三取代[3+2]環化加成產物－1,2,3-triazole，此反應條件溫和，不需金屬的參與，為有效合成 1,2,3-triazole 的途徑；此外，本反應之產物雜環架構中的 4 號位置為酯類取代基，可經由還原、取代等反應轉換為多樣化之官能基，在有機合成上的應用性廣泛。

Table 3. DBU-promoted [3+2] cycloaddition reaction.[a]



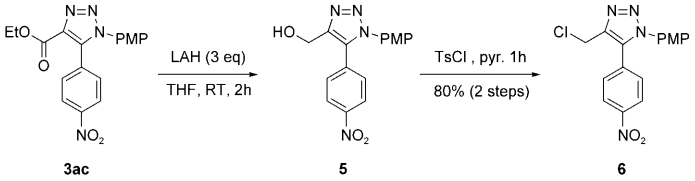
Entry	1	R^2	Product	T [°C]	t [h]	Yield (3:4) [%][b]
1	**1a**	*o*-NO_2-Ph (**2a**)	**3aa**	RT	2	90
2	**1a**	*m*-NO_2-Ph (**2b**)	**3ab**	RT	2	90 (72:18)
3	**1a**	*p*-NO_2-Ph (**2c**)	**3ac**	RT	2	95 (80:15)
4	**1a**	*p*-CN-Ph (**2d**)	**3ad**	RT	4	86 (61:25)
5	**1a**	*p*-CF_3-Ph (**2e**)	**3ae**	RT	21	81
6	**1a**	Ph (**2f**)	**3af**	RT	24	87 (70:17)
7	**1a**	*p*-F-Ph (**2g**)	**3ag**	RT	21	77
8	**1a**	*p*-Cl-Ph (**2h**)	**3ah**	50	24	60
9	**1a**	*p*-Br-Ph (**2i**)	**3ai**	50	24	64
10	**1a**	*o*-Me-Ph (**2j**)	**3aj**	50	24	67
11	**1a**	*p*-Me-Ph (**2k**)	**3ak**	50	24	64
12	**1a**	2-pyridinyl (**2l**)	**3al**	50	4	83
13	**1a**	3-pyridinyl (**2m**)	**3am**	50	4	75
14	**1b**	**2c**	**3bc**	RT	24	75
15	**1b**	**2d**	**3bd**	RT	24	75

[a] Reaction conditions: *N*-PMP aryl imine (1.92 mmol, 4.0 equiv) was dissolved in CH_3CN (2.5 mL), and then ethyl diazoacetate (0.48 mmol) and DBU (3.0 equiv) were added. [b] Yield of isolated product.

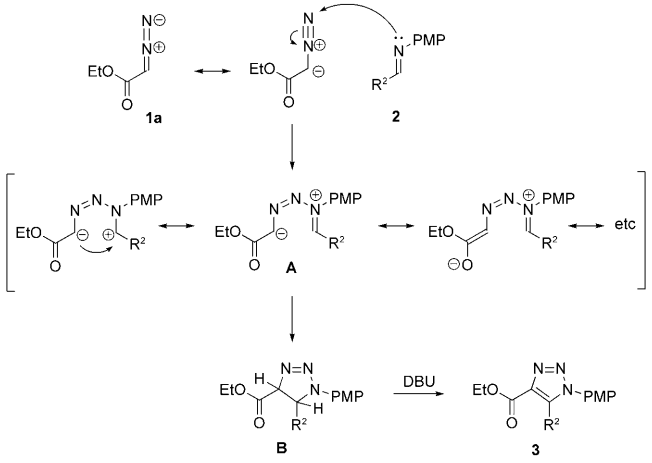
result demonstrated that the ester and amide linkage of diazo compounds are effective for the cycloaddition reaction.

The exact mechanism for this transformation is not currently clear, but a proposed mechanism is given in Scheme 1. It is believed that the addition of *N*-PMP arylimine nitrogen atom in **2** to the terminal diazo nitrogen atom to give a zwitterionic species (**A**). The zwitterionic species is stabilized by the many possible resonance forms, as well as the use of a polar aprotic solvent (CH_3CN). A cyclization reaction then forms triazoline heterocycle **B**. Subsequently, base-mediated elimination/aromatization gives the desired 1,2,3-triazole.[16] For some poor-electron-donating aryl imines, elevated temperature is required to promote the process (Table 3, entries 8–13). The generation of the known *N*-PMP amide **4** may come from the hydrolysis of the heterocycle intermediates during the elimination/workup process.[17]

To demonstrate the utility of this methodology, the newly synthesized carboxylate group containing 1,2,3-triazole **3ac** was transformed into its chloride **6**. Treatment of **3ac** with lithium aluminum hydride (LAH) in THF afforded the corresponding primary alcohol, which was treated with toluene-*p*-sulfonyl chloride (TsCl) in pyridine to give **6** in an overall chemical yield of 80% (Scheme 2). The structure of compound **6** was confirmed by X-ray analysis.[14]



Scheme 2. Synthetic application of ethyl 1-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate (**3ac**).



Scheme 1. Proposed mechanism for the formation of the fully substituted 1,2,3-triazole.

Conclusions

In summary, a convenient and direct assembly of fully substituted 1,2,3-triazoles is presented for the first time. Ethyl diazoacetate was treated with aryl imines in the presence of DBU to provide ethyl 1-(4-methoxyphenyl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylates in good to high chemical yields under mild reaction conditions. The installation of the carbonyl functionality in the 1,2,3-triazole nucleus allows further chemical transformation. The structures of the products were well characterized and a reasonable mechanism was proposed. Further development of triazoles synthesis is underway.

Experimental Section

Infrared spectra were obtained using a Perkin–Elmer Spectrum RX spectrometer using thin films of products coated on NaCl plates. Only absorption frequencies higher than 1200 cm^{-1} are reported. ^1H and ^{13}C NMR spectra were measured on the Bruker Avance 400 MHz instruments, and spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard using $CDCl_3$ as solvent. High-resolution mass spectrometry (HRMS; EI) analysis was performed at the Department of Chemistry, National Chung Hsing University. The X-ray crystal structures were obtained at the National Taiwan Normal University for Crystallographic Studies. Melting points were taken on Fargo MP-1D or EZ-Melt apparatus without correction. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck precoated TLC plates (silica gel 60 F254). The products were purified by flash column chromatography silica gel 60 (Merck, 230–400 mesh) using the indicated eluent.

All *p*-methoxyphenyl (PMP) imines **2a**–**m** were prepared from *p*-anisidine and the corresponding aldehydes according to the literature method.[18] Commercially obtained reagents were used as received.

Preparation of *N*-phenylcamphor pyrazolidinone derived α-acetamide (**1b**):[19] Glyoxylic acid *p*-toluenesulfonyl hydrazone (2.84 g, 11.7 mmol) was heated at reflux with thionyl chloride (12 mL) at 70 °C for 2 h under a nitrogen atmosphere. Excess $SOCl_2$ was removed by evaporation to give the corresponding acid chloride as a yellowish solid. To a solution of *N*-phenylcamphor pyrazolidinone (1.00 g, 3.9 mmol) in CH_2Cl_2 at 0 °C was added a solution of the freshly prepared acid chloride in CH_2Cl_2 dropwise. The mixture was stirred for 10 min, and then triethylamine (4.0 mL, 27.8 mmol) was added dropwise to the reaction solution. Stirring was continued for 30 min at 0 °C and then for 30 min at room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and Na_2CO_3 and then extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate = 4:1) to give the title compound as a yellowish solid (1.09 g, 86 %). R_f = 0.38 (hexanes/EtOAc 3:1); m.p.: 120–122 °C; FTIR: $\tilde{\nu}$ = 3116, 2996, 2960, 2111, 1719, 1664, 1596, 1490, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.36 (m, 4H), 7.19 (t, J = 7.1 Hz, 1H), 4.73 (s, 1H), 4.01 (dd, J = 8.1, 4.8 Hz, 1H), 2.71 (ddd, J = 13.5, 7.2, 3.5 Hz, 1H), 2.27 (td, J = 11.6, 4.8 Hz, 1H), 2.11–1.96 (m, 3H), 1.51–1.45 (m, 1H), 1.42–1.36 (m, 1H), 1.10 (s, 3H), 1.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 169.8, 139.1, 128.9, 125.6, 120.7, 67.7, 58.8, 54.1, 49.2, 46.3, 38.5, 28.3, 27.0, 20.5, 20.1 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{20}N_4O_2$: 324.1586; found: 324.1582.

General procedure for DBU-mediated cycloaddition: To a stirred solution of *N*-PMP aryl imine (1.92 mmol) in MeCN (2.5 mL) was added ethyl diazoacetate (0.48 mmol) at the specified temperature. The mixture was stirred for 2 min and then DBU (1.44 mmol) was added dropwise. Stirring was continued until the starting material disappeared completely upon inspection by TLC. The solvent was removed under reduced pressure, and the product was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate = 4:1 to 2:1) to give the corresponding 1,2,3-triazoles as a yellowish solid. The solid was recrystallized from hexanes/EtOAc.

3aa: Pale-yellowish crystal; R_f = 0.47 (hexanes/EtOAc 1:1); m.p.: 168–171 °C; FTIR: $\tilde{\nu}$ = 3074, 2982, 2936, 2841, 1736, 1610, 1578, 1530, 1516, 1351, 1255, 1225, 1208 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.17 (m, 1H), 7.66–7.61 (m, 2H), 7.27 (d, J = 8.9 Hz, 2H), 7.24–7.22 (m, 1H), 6.86 (d, J = 8.9 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.25 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 160.5, 148.7, 137.9, 136.7, 133.3, 132.3, 131.1, 128.2, 126.4, 125.0, 122.6, 114.6, 61.4, 55.5, 14.0 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}N_4O_5$: 368.1121, found: 368.1113; crystal data for **3aa** at 200(2) K; $C_{18}H_{16}N_4O_5$, M_r = 368.35; triclinic, $P\bar{1}$; a = 8.8287(2), b = 10.0418(2), c = 10.6487(2) Å; α = 104.7160(10), β = 103.3140(10), γ = 100.3250(10)°; V = 859.75(3) $Å^3$, F_{000} = 384; λ = 0.71073 Å, Z = 2, D = 1.423 $Mg\,m^{-3}$, μ = 0.107 mm^{-1}, 9904 reflections, 0 restraints, 245 parameters, R = 0.0539, Rw = 0.1272 for all data.

3ab: Pale-yellowish crystal; R_f = 0.21 (hexanes/EtOAc 2:1); m.p.: 163–165 °C; FTIR: $\tilde{\nu}$ = 3081, 2983, 2934, 2840, 1725, 1668, 1608, 1530, 1515, 1351, 1252, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (dt, J = 8.0, 1.9 Hz, 1H), 8.23–8.22 (m, 1H), 7.63–7.55 (m, 2H), 7.19 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.34 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 160.7, 147.9, 138.5, 137.3, 136.2, 129.4, 127.9, 127.8, 126.8, 125.6, 124.6, 114.8, 61.5, 55.6, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}N_4O_5$: 368.1121, found: 368.1113; crystal data for **3ab** at 296(2) K; $C_{18}H_{16}N_4O_5$, M_r = 368.35; monoclinic, $P2/c$; a = 24.2894(18), b = 6.6791(5), c = 25.8889(18) Å; β = 111.850(4)°; V = 3898.3(5) $Å^3$, F_{000} = 1536; λ = 0.71073 Å, Z = 8, D = 1.255 $Mg\,m^{-3}$, μ = 0.094 mm^{-1}, 25253 reflections, 0 restraints, 481 parameters, R = 0.2936, Rw = 0.3385 for all data.

3ac: Brownish crystal; R_f = 0.26 (hexanes/EtOAc 2:1); m.p.: 133–134 °C; FTIR: $\tilde{\nu}$ = 3110, 2984, 2938, 2843, 1732, 1606, 1591, 1520, 1348, 1254, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.33 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 160.6, 148.4, 138.6, 137.2, 132.5, 131.6, 127.9, 126.6, 123.4, 114.7, 61.5, 55.6, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}N_4O_5$: 368.1121; found: 368.1127.

3ad: Yellowish oil; R_f = 0.21 (hexanes/EtOAc 2:1); FTIR: $\tilde{\nu}$ = 3060, 2916, 2850, 2231, 1730, 1609, 1591, 1516, 1498, 1379, 1254, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.35 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 160.6, 138.9, 137.2, 132.0, 131.2, 130.7, 128.1, 126.6, 117.9, 114.7, 113.8, 61.5, 55.6, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{19}H_{16}N_4O_3$: 348.1222; found: 348.1229.

3ae: Brownish crystal; R_f = 0.33 (hexanes/EtOAc 3:1); m.p.: 127–128 °C; FTIR: $\tilde{\nu}$ = 3066, 2988, 2930, 2843, 1732, 1610, 1592, 1517, 1327, 1255, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.34 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 160.5, 139.4, 137.1, 132.0, 131.6, 130.8, 129.7, 128.3, 126.6, 125.3 (q, J = 4 Hz, **C**-CF_3), 123.6 (q, J = 271 Hz, **C**F_3), 61.4, 55.6, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{19}H_{16}F_3N_3O_3$: 391.1144; found: 391.1149.

3af: Brownish crystal; R_f = 0.28 (hexanes/EtOAc 3:1); m.p.: 108–110 °C; FTIR: $\tilde{\nu}$ = 3056, 2923, 2857, 1729, 1610, 1591, 1516, 1378, 1253, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 3H), 7.30–7.27 (m, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.32 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 160.2, 140.8, 136.8, 130.3, 129.8, 128.8, 128.3, 126.6, 125.9, 114.4, 61.1, 55.5, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{17}N_3O_3$: 323.1270; found: 323.1277.

3ag: Brownish oil; R_f = 0.28 (hexanes/EtOAc 3:1); FTIR: $\tilde{\nu}$ = 3072, 2926, 2842, 1732, 1610, 1593, 1516, 1504, 1379, 1254, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.07 (t, J = 8.6 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.35 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4 (d, J = 250 Hz), 161.0, 160.3, 139.9, 136.8, 132.4 (d, J = 8 Hz), 128.6, 126.6, 121.8 (d, J = 4 Hz), 115.7 (d, J = 22 Hz), 114.5, 61.2, 55.5, 14.2 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}FN_3O_3$: 341.1176; found: 341.1184.

3ah: Brownish solid; R_f = 0.33 (hexanes/EtOAc 3:1); m.p.: 126–127 °C; FTIR: $\tilde{\nu}$ = 3062, 2982, 2936, 2841, 1732, 1608, 1590, 1516, 1488, 1378, 1254, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 1.34 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 160.3, 139.7, 136.8, 136.1, 131.6, 128.6, 128.4, 126.6, 124.2, 114.5, 61.2, 55.5, 14.1 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}ClN_3O_3$: 357.0880; found: 357.0883.

3ai: Brownish oil; R_f = 0.32 (hexanes/EtOAc 3:1); FTIR: $\tilde{\nu}$ = 2959, 2925, 2854, 1732, 1609, 1590, 1516, 1485, 1378, 1254, 1215 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.4 Hz, 2H), 7.18–7.16 (m, 4H), 6.89 (d, J = 9.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.35 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 160.4, 139.8, 136.8,

131.9, 131.7, 128.4, 126.6, 124.8, 124.5, 114.6, 61.3, 55.6, 14.2 ppm; HRMS (EI) m/z calcd. for $C_{18}H_{16}BrN_3O_3$ 401.0375; found 401.0366.

3aj: Brownish crystal; $R_f = 0.33$ (hexanes/EtOAc 3:1); m.p.: 109–110 °C; FTIR: $\tilde{\nu} = 2924, 2911, 2902, 2837, 1729, 1609, 1516, 1379, 1254, 1215\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (td, $J = 7.5$, 1.3 Hz, 1H), 7.24–7.14 (m, 5H), 6.83 (d, $J = 9.0$ Hz, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 1.99 (s, 3H), 1.26 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.8, 160.1, 140.5, 137.6, 137.4, 130.3, 130.0, 128.9, 126.2, 125.8, 125.6, 114.4, 61.0, 55.5, 19.7, 14.0$ ppm; HRMS (EI) m/z calcd. for $C_{19}H_{19}N_3O_3$: 337.1426; found: 337.1422.

3ak: Brownish oil; $R_f = 0.31$ (hexanes/EtOAc 3:1); FTIR: $\tilde{\nu} = 2985, 2903, 2841, 1727, 1610, 1516, 1378, 1253, 1214\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$–7.17 (m, 6H), 6.87 (d, $J = 9.0$ Hz, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 2.36 (s, 3H), 1.34 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.1, 160.1, 141.0, 140.0, 136.7, 130.1, 129.0, 128.9, 126.6, 122.7, 114.4, 61.1, 55.5, 21.4, 14.2$ ppm; HRMS (EI) m/z calcd. for $C_{19}H_{19}N_3O_3$: 337.1426; found: 337.1424.

3al: Colorless crystal; $R_f = 0.37$ (hexanes/EtOAc 1:1); m.p.: 166–168 °C; FTIR: $\tilde{\nu} = 2995, 2936, 2854, 1731, 1609, 1591, 1516, 1465, 1253, 1221\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.61$ (d, $J = 4.4$ Hz, 1H), 7.78 (td, $J = 7.8$, 1.7 Hz, 1H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.35–7.32 (m, 1H), 7.25 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.36 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 1.31 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.8, 160.2, 149.7, 146.3, 139.7, 137.4, 136.3, 129.0, 126.5, 126.4, 124.1, 114.2, 61.2, 55.5, 14.1$ ppm; HRMS (EI) m/z calcd. for $C_{17}H_{16}N_4O_3$: 324.1222, found: 324.1213; crystal data for **3al** at 293(2) K; $C_{17}H_{16}N_4O_3$, $M_r = 324.34$; monoclinic, $P21/n$; $a = 8.1644(2)$, $b = 14.4846(5)$, $c = 13.5393(4)$ Å; $\beta = 93.844(2)°$; $V = 1597.53(8)$ Å^3; $F_{000} = 680$; $\lambda = 0.71073$ Å, $Z = 4$, $D = 1.349\ Mg\,m^{-3}$, $\mu = 0.095\ mm^{-1}$, 7594 reflections, 0 restraints, 217 parameters, $R = 0.0753$, $Rw = 0.1505$ for all data.

3am: Brownish solid; $R_f = 0.26$ (hexanes/EtOAc 1:1); m.p.: 115–117 °C; FTIR: $\tilde{\nu} = 2961, 2924, 2851, 1732, 1668, 1608, 1590, 1516, 1254, 1220\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.64$ (d, $J = 4.1$ Hz, 1H), 8.50 (s, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.35 (dd, $J = 7.9$, 4.1 Hz, 1H), 7.19 (d, $J = 9.0$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 1.34 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.8, 160.5, 150.6, 150.4, 137.8, 137.8, 137.4, 128.1, 126.8, 123.0, 122.5, 114.7, 61.4, 55.6, 14.1$ ppm; HRMS (EI) m/z calcd. for $C_{17}H_{16}N_4O_3$: 324.1222; found: 324.1228.

3bc: Yellowish solid; $R_f = 0.20$ (hexanes/EtOAc 2:1); m.p.: 168–170 °C; FTIR: $\tilde{\nu} = 3058, 2963, 2939, 2842, 1720, 1655, 1604, 1517, 1492, 1458, 1347, 1303, 1255\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (d, $J = 8.6$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 7.8$ Hz, 2H), 7.33 (t, $J = 7.8$ Hz, 2H), 7.18–7.16 (m, 3H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.81 (dd, $J = 7.2$, 4.9 Hz, 1H), 3.84 (s, 3H), 2.31 (td, $J = 11.9$, 5.0 Hz, 1H), 2.22–2.17 (m, 1H), 2.03–1.99 (m, 1H), 1.93–1.88 (m, 2H), 1.58–1.52 (m, 1H), 1.43–1.37 (m, 1H), 1.19 (s, 3H), 1.16 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3, 160.8, 156.0, 148.3, 139.7, 137.6, 137.5, 131.9, 131.4, 128.6, 128.1, 126.6, 126.1, 123.6, 121.7, 114.9, 70.4, 59.6, 55.7, 51.9, 47.1, 39.1, 28.6, 26.6, 20.6, 20.1$ ppm; MS (EI) m/z (%): 578 (M^+, 25), 323 (16), 295 (33), 255 (100), 249 (23); HRMS (EI) m/z calcd. for $C_{32}H_{30}N_6O_5$: 578.2278; found: 578.2280.

3bd: Yellowish solid; $R_f = 0.16$ (hexanes/EtOAc 2:1); m.p.: 167–169 °C; FTIR: $\tilde{\nu} = 3058, 2961, 2938, 2842, 2231, 1722, 1658, 1609, 1593, 1515, 1496, 1360, 1303, 1255\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (d, $J = 6.6$ Hz, 2H), 7.41–7.38 (m, 4H), 7.32 (t, $J = 6.6$ Hz, 2H), 7.16–7.13 (m, 3H), 6.92 (d, $J = 7.1$ Hz, 2H), 4.80 (m, 1H), 3.83 (s, 3H), 2.29 (td, $J = 9.6$, 4.1 Hz, 1H), 2.21–2.18 (m, 1H), 2.03–1.98 (m, 1H), 1.92 (t, $J = 3.0$ Hz, 1H), 1.88 (dd, $J = 11.0$, 6.4 Hz, 1H), 1.56–1.51 (m, 1H), 1.41–1.36 (m, 1H), 1.19 (s, 3H), 1.15 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.1, 160.5, 156.0, 139.3, 137.6, 137.5, 132.0, 130.8, 129.9, 128.4, 128.0, 126.4, 125.8, 121.5, 117.7, 114.7, 113.4, 70.2, 59.5, 55.5, 51.8, 46.9, 38.9, 28.4, 26.5, 20.4, 19.9$ ppm; MS (EI) m/z (%): 558 (M^+, 22), 303 (23), 276 (71), 255 (100), 235 (22), 205 (10); HRMS (EI) m/z calcd. for $C_{33}H_{30}N_6O_3$: 558.2379; found: 558.2377.

4b:[20] Colorless crystal; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.69$ (s, 1H), 8.41 (d, $J = 7.6$ Hz, 1H), 8.26 (d, $J = 7.6$ Hz, 1H), 7.85 (br s, NH), 7.71 (t, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.2, 148.3, 136.7, 133.3, 130.2, 130.1, 126.3, 122.4, 121.7, 114.4, 55.5$ ppm; MS (EI) m/z (%): 272 (M^+, 100), 150 (48), 124 (40).

4c:[21] Dark-yellowish solid; m.p.: 190–192 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.34$ (d, $J = 8.6$ Hz, 2H), 8.03 (d, $J = 8.6$ Hz, 2H), 7.76 (br s, NH), 7.54 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.2, 140.6, 130.3, 128.2, 124.0, 122.3, 116.4, 114.9, 114.4, 55.5$ ppm; MS (EI) m/z (%): 272 (M^+, 100), 150 (16), 122 (15).

4d: Brownish solid; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 8.0$ Hz, 2H), 7.81 (br s, NH), 7.78 (d, $J = 8.0$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.7, 157.1, 139.0, 132.6, 130.3, 127.7, 122.3, 117.9, 115.3, 114.4, 55.5$ ppm; MS (EI) m/z (%): 252 (M^+, 100), 130 (24), 122 (14).

4f:[21] Brownish solid; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (d, $J = 7.2$ Hz, 2H), 7.74 (br s, NH), 7.55–7.46 (m, 5H), 6.91 (d, $J = 9.0$ Hz, 2H), 3.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.7, 135.1, 131.7, 131.0, 128.8, 127.0, 122.1, 114.3, 55.5$ ppm; MS (ESI), m/z: 477 [$2M$ + Na]$^+$.

Preparation of {1-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl}methanol (**5**): To a stirred suspension of LAH (20 mg, 0.50 mmol) in dry THF (0.5 mL) at room temperature was added a solution of triazole **3ac** (50 mg, 0.14 mmol) in dry THF (0.5 mL) dropwise under a nitrogen atmosphere. The solution was stirred for 2 h and then 15% aqueous NaOH (5 mL) and H_2O (5 mL) were added. The reaction was further diluted with diethyl ether, filtered through a pad of Celite, and the filtered bed was thoroughly washed with diethyl ether. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate = 1:1) to give the title compound as a colorless liquid (40 mg, 90%); $R_f = 0.24$ (hexanes/EtOAc 1:1); FTIR: $\tilde{\nu} = 3333, 2930, 2869, 2853, 1605, 1519, 1345, 1256\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 8.6$ Hz, 2H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.20 (d, $J = 8.8$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 4.81 (s, 2H), 4.29 (br s, OH), 3.84 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.4, 147.9, 145.7, 133.8, 133.0, 130.5, 128.8, 126.5, 123.9, 114.7, 55.5, 55.3$ ppm; MS (EI) m/z (%): 326 (M^+, 29), 298 (94), 281 (100), 268 (27), 108 (19); HRMS (EI) m/z calcd. for $C_{16}H_{14}N_4O_4$: 326.1015, found: 326.1008.

Preparation of 4-(chloromethyl)-1-(4-methoxyphenyl)-5-(4-nitrophenyl)-1*H*-1,2,3-triazole (**6**): A solution of the primary alcohol **5** (60 mg, 0.18 mmol) and TsCl (0.17 g, 0.89 mmol) in pyridine (1.2 mL) was stirred at 0 °C for 2 h and then at room temperature for 24 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were then washed with 2.4 M aqueous HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluting with hexanes/ethyl acetate = 3:1) and then recrystallized from hexanes/EtOAc to give **6** (56.34 mg, 89%) as a colorless crystal; $R_f = 0.33$ (hexanes/EtOAc 3:1); m.p.: 160–162 °C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$ (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 9.0$ Hz, 2H), 6.93 (d, $J = 9.0$ Hz, 2H), 4.74 (s, 2H), 3.84 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 160.5, 148.3, 142.6, 133.8, 132.7, 130.4, 128.7, 126.5, 124.2, 114.8, 55.6, 35.9$ ppm; MS (EI) m/z (%): 344 (M^+, 7), 281 (100), 134 (7); HRMS (EI) m/z calcd. for $C_{16}H_{13}ClN_4O_3$: 344.0676, found: 344.0670; crystal data for **6** at 200(2) K; $C_{16}H_{13}ClN_4O_3$, $M_r = 344.75$; monoclinic, $C2/c$; $a = 14.3184(4)$, $b = 10.6488(3)$, $c = 20.4476(6)$ Å; $\beta = 91.0100(10)°$; $V = 3117.24(15)$ Å^3, $F_{000} = 1424$; $\lambda = 0.71073$ Å, $Z = 8$, $D = 1.469\ Mg\,m^{-3}$, $\mu = 0.268\ mm^{-1}$, 8322 reflections, 0 restraints, 217 parameters, $R = 0.0618$, $Rw = 0.1336$ for all data.

Acknowledgements

We thank the National Science Council of the Republic of China (NSC 96-2113-M-003-005-MY3) for its financial support of this work. Our gratitude extends to the Academic Paper Editing Clinic at NTNU, and to the

National Center for High-Performance Computing for providing us with computer time and facilities.

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Received: July 28, 2009
Published online: December 22, 2009

