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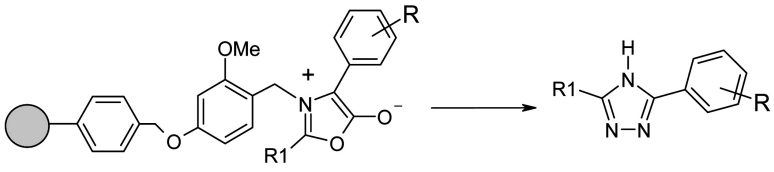

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Polymer-Supported 1,3-Oxazolium-5-olates: Synthesis of 1,2,4-Triazoles

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A traceless synthesis of 3,5-disubstituted 1,2,4-triazoles has been developed on polymeric supports. The synthetic process utilizes immobilized mesoionic 1,3-oxazolium-5-olates (münchnones) as key intermediates in the 1,3-dipolar cycloaddition reaction. The initial step in the synthesis involves reductive alkylation of phenylglycine methyl esters with Ameba resin. The resulting immobilized amino acid esters were subsequently acylated with a variety of carboxylic acid chlorides and subjected to hydrolysis with 15% KOH to yield the polymer-bound carboxylic acids. Finally, the cycloaddition between diethyl diazocarboxylate or 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione and the polymer-bound münchnones generated from the corresponding carboxylic acids afforded the polymer-bound 3,5-disubstituted 1,2,4-triazoles. Cleavage from the polymeric support using trifluoroacetic acid gave the desired 3,5-disubstituted 1,2,4-triazoles with excellent yield and high purity.

Introduction

Several biologically active therapeutics contain five-membered ring heterocycles in their chemical structures. The 1,2,4-triazole moiety is present, for example, in certain antiasthmatic,[1] antiviral (ribavirin),[2] antifungal (fluconazole),[3] antibacterial,[4] and hypnotic[5] (triazolam) drugs. Owing to its broad spectrum of biological activity,[6−12] the 1,2,4-triazole ring system represents an attractive target for the elaboration of solid-phase synthesis methodology and the production of combinatorial libraries.

There are, so far, only a few published studies about the solid-phase synthesis of substituted 1,2,4-triazoles. Katritzky reported the synthesis of trisubstituted 1,2,4-triazoles on a solid support based on the condensation reaction between an acyl hydrazide Wang resin and substituted amidines.[13] The yields were nearly quantitative, but the purities were 37−90%, depending on the substituents of the triazole core. This procedure enables the alkylation of the 1-position, giving the trisubstituted 1,2,4-triazoles, but suffers from the nontraceless nature of the reaction sequence. Hence, the synthesized 1,2,4-triazoles contain the 4-hydroxyphenyl linker of the starting Wang resin.[13] Fehrentz and co-workers prepared, in turn, 3,4,5-trisubstituted 1,2,4-triazoles on solid supports.[14] Their four-step synthesis protocol was based on the three-day reaction between the polymer-bound thioamides and substituted acyl hydrazides in the presence of toxic mercury(II)acetate. After cleavage, the 1,2,4-triazoles were obtained in good or excellent purity.[14] The Makara group has synthesized 3-alkylamino-1,2,4-triazoles by means of a regioselective cyclization reaction between immobilized *N*-acyl-1*H*-benzotriazole-1-carboximidamides and hydrazines in moderate yield but high purity.[15] Paulvannan et al. synthesized 1,3,5-trisubstituted 1,2,4-triazoles on solid supports using mild oxidizing agents, such as chlorates, Dess−Martin periodinane and tetrapropylammonium perruthenate/*N*-methylmorpholine oxide in an oxidative cyclization reaction of 1,2,4-triazenes. Their six-step synthesis protocol gave 1,2,4-triazoles in 16−47% yield. The method suffers from the nontraceless nature of the reaction sequence in which the Wang resin-derived 4-hydroxyphenyl appendage remains attached to the 3-position of the 1,2,4-triazole nucleus.[16] The Houghten group synthesized 3-amino-1,2,4-triazoles on solid support by the reaction of immobilized *S*-methyl-*N*-acyl-isothioureas with hydrazines under mild conditions. Starting from 4-nitrophenyl carbonate resin, the 3-amino-1,2,4-triazoles were obtained in moderate yields (58−75%).[17] Katritzky and co-workers also synthesized 3-amino-1,2,4-triazoles in moderate to good yields (69−88%). They used a condensation reaction between the resin-bound *S*-methyl-*N*-acylisothioureas and hydrazines in refluxing acetonitrile.[18] Rostamizadeh et al. reported, in turn, a solid-phase synthesis of 1,2,4-triazoles under microwave irradiation. They used a three-component condensation protocol, in which carboxylic acid hydrazide, *S*-methyl isothioamide hydroiodide, and ammonium acetate were allowed to react on the surface of the silica gel under microwave irradiation. Moderate to good yields (66−91%) of 1,2,4-triazoles were obtained with a reaction time of only 2−10 min.[19] Finally, Larsen et al. synthesized the 5-aryl-3-arylthiomethyl-1,2,4-triazoles from amidrazones by a traceless method using 4-benzyloxy-2-methoxybenzylamine resin. After the seven-step reaction sequence, the purity of the compounds was 37−96%, but the yields were moderate (13−36%).[20]

The Huisgen group was the first to report the synthesis of 1,2,4-triazoles by the reaction of münchnones with diethyl

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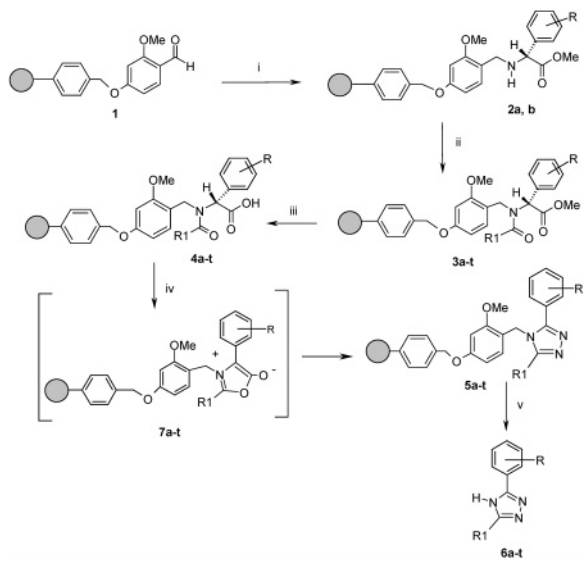
Scheme 1[a]



[a] Reagents and conditions: (i) $NaB(OAc)_3H$ (4 equiv), (*R*)-(−)-2-phenylglycine methyl ester (**a**, 4 equiv) or (*R*)-(−)-2-(*o*-chlorophenyl)glycine methyl ester (**b**, 4 equiv), 1% HOAc/DMF, rt, 12 h; (ii) *N*,*N*-diisopropylethylamine (2 equiv), R_1COCl (10 equiv), CH_2Cl_2, rt, 12 h; (iii) 15% KOH in 1,4-dioxane/water (3:1), 120 °C, 3.5 h; (iv) Ac_2O, DEAD or 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (3 equiv), CH_2Cl_2, rt, 8 h; (v) 30% TFA/CH_2Cl_2, rt, 1.5 h.

azodicarboxylate (DEAD) in solution.[21] We have successfully translated this solution-phase synthesis onto the solid phase. One of the key advantages of this sequence is the use of a new 1,2,4-triazole linking method in which the resin handle is attached to the nitrogen atom of the starting amino acid ester so that it ends up being the *N*-4 nitrogen of the final product.[20] This facilitates an effective cycloaddition and isolation of the product 1,2,4-triazoles and enables the derivatization of the triazole core with a variety of substituents.

Results and Discussion

Commercially available Ameba resin[22] (1% DVB, 100−200 mesh, 1.0−1.5 mmol/g) **1** was treated with (*R*)-(−)-2-phenylglycine methyl ester (**a**, 4 equiv) or (*R*)-(−)-2-(*o*-chlorophenyl)glycine methyl ester (**b**, 4 equiv) in the presence of sodium triacetoxyborohydride (Scheme 1). This reductive alkylation was followed until the aldehyde functionality was fully consumed[23] to produce the resin **2a**−**b**. The progress of the reaction was monitored by means of FT-IR spectrometry and a qualitative 2,4-dinitrophenylhydrazide test.[24] The yield of the reductive alkylation procedure was quantitative, and the product resins **2a**−**b** were gray in color.

Intermediates **2a**−**b** were acylated efficiently with a variety of carboxylic acid chlorides (10 equiv) in the presence of *N*,*N*-diisopropylethylamine as a base in dichloromethane (rt, 12 h). The excess of acylating reagent was washed easily out to yield resins **3a**−**t**, which were characterized by two sharp FT-IR absorption bands at 1694 cm^{-1} (C═O) and 1769 cm^{-1} (C═O). The resulting α-amidoesters **3a**−**t** were subjected to KOH hydrolysis to provide polymer-bound carboxylic acids **4a**−**t** (Scheme 1), which were conveniently distinguished by two sharp FT-IR absorption bands at 1690 cm^{-1} (C═O) and 1730 cm^{-1} (C═O).[25]

Table 1. Preparation of the 3,5-Disubstituted 1,2,4-Triazoles (**6**) via Polymer-Bound 1,3-Oxazolium-5-olates (Münchnones)

entry	1,2,4-triazole	R	R1	Yield[a] (%)	Purity[b] (%)
1	**6a**	H	4-$MeOC_6H_4$	92	83
2	**6b**	H	4-MeC_6H_4	91	80
3	**6c**	H	C_6H_5	90	89
4	**6d**	H	4-PnC_6H_4	93	81
5	**6e**	H	4-PrC_6H_4	91	85
6	**6f**	H	4-FC_6H_4	90	82
7	**6g**	H	3-pyridyl	93	95
8	**6h**	H	2-naphthyl	94	89
9	**6i**	H	4-$NO_2C_6H_4$	83	74
10	**6j**	H	4-ClC_6H_4	90	79
11	**6k**	H	4-EtC_6H_4	92	77
12	**6l**	2-Cl	4-MeC_6H_4	85	78
13	**6m**	2-Cl	4-EtC_6H_4	95	86
14	**6n**	2-Cl	3-pyridyl	90	80
15	**6o**	2-Cl	4-FC_6H_4	89	75
16	**6p**	2-Cl	4-$NO_2C_6H_4$	85	71
17	**6q**	2-Cl	4-PrC_6H_4	92	83
18	**6r**	2-Cl	4-ClC_6H_4	91	81
19	**6s**	2-Cl	4-$MeOC_6H_4$	87	73
20	**6t**	2-Cl	2-naphthyl	96	98

[a] The yields are based on the original loading of the resin (1.25 mmol/g). [b] Purities were determined by ^1H NMR and LC/MS (280 nm).

Treatment of carboxylic acids **4a**−**t** with DEAD in the presence of acetic anhydride at room temperature initially resulted in formation of the intermediate 1,3-oxazolium-5-olates **7a**−**t** (Scheme 1). Subsequent 1,3-dipolar cycloaddition of the münchnones with DEAD, followed by the concomitant elimination of carbon dioxide from the intermediate cycloadduct, provided the polymer-bound 1,2,4-triazoles **5a**−**t** with excellent yield and high purity (Table 1).

When compounds **5a**−**t** were treated with TFA, the product triazoles **6a**−**t** were obtained in excellent yields (83−96%). The cleavage process was repeated two to three times because initial cleavage was found to be incomplete. Products[26] were recovered in excellent yield (calculated on the basis of the original loading of the resin, 1.25 mmol/g) after cleavage and purification with SiO_2 column chromatography (see Table 1).

We also wanted to study this reaction sequence by using amino acid esters with nonaromatic substituents in the 2-position. In the final step, the reaction failed to produce the desired 1,2,4-triazoles when the substituent was methyl. This may have been due to the presence of the aromatic substituent on the intermediate münchnone, which helps to stabilize it and promote the 1,3-dipolar cycloaddition reaction. We believe that in the presence of an alkyl group, the +I effect destabilizes the intermediate, with the result that 1,3-dipolar cycloaddition reaction does not proceed to give the 1,2,4-triazoles.

Finally, we investigated other diazo dicarbonyl compounds as dipolarophiles instead of DEAD. The final step of this reaction sequence was carried out in the presence of 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (3 equiv), which led to shorter reaction times. Moreover, the yields were slightly better when compared to those obtained using DEAD (Table 1).

Conclusion

In conclusion, we have developed an expedient synthesis sequence for effective preparation of the 3,5-disubstituted 1,2,4-triazoles using polymer-supported münchnones. This reaction methodology also employs a new linking strategy in which the resin handle is attached directly to *N*-4 of the triazole core, as previously shown by Larsen, who developed the first traceless solid-phase synthesis of 1,2,4-triazoles by means of a nucleophilic cyclization mechanism.[20] Thus, the substituents in different positions on the 1,2,4-triazole core can be varied independently. The process utilizes a 1,3-dipolar cycloaddition reaction with polymer-supported münchnones as key intermediates. This reaction was also carried out in the presence of 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione, which led to slightly improved results when compared with DEAD. This five-step procedure offers an efficient, *traceless* synthesis of 3,5-disubstituted 1,2,4-triazoles, complementing the known methods that provide trisubstituted 1,2,4-triazoles on solid support. We are continuing our studies by constructing a library of 1,2,4-triazoles by means of a 1,3-dipolar cycloaddition reaction using immobilized münchnones as dipolar reaction partners.

Experimental Section

All chemicals were obtained from commercial suppliers and were of reagent grade. A parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station. Catalogue No. RR 99900) was used for the synthesis of the compounds, and the reactions were run under argon atmosphere. Melting points were obtained with a Bibby Stuart Scientific SMP3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 300 Plus spectrometer. Chemical shifts (δ) are reported in parts per million relative to the NMR solvent signal (CD_3OD, 3.31 ppm for proton and 49.15 ppm for carbon NMR spectra and DMSO-d_6, 2.51 ppm for proton and 39.51 ppm for carbon NMR spectra). FT-IR spectra of the products were recorded on a Bruker Vertex 70 FT-IR spectrometer equipped with the Harrick MVP2-unit. GC/MS analyses were performed with a Hewlett-Packard gas chromatograph 5890A connected to the 5970 series mass-selective detector. HPLC/MS analyses were performed with an HP1100 instrument with UV detector wavelength of 280 nm and Merck Chromolith SpeedROD RP-18 (50 mm × 4.6 mm) column and an API 3000 triple quadrupole LC/MS/MS mass spectrometer with TurboIonSpray ion source. The resin was purchased from Sigma-Aldrich, Ameba resin (4-hydroxy-2-methoxybenzaldehyde, polymer-bound, 100−200 mesh, 1−1.5 mmol/g) cross-linked with 1% DVB. Thin-layer chromatography (TLC) was performed with Merck TLC aluminum supported plates, silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (0.040−0.063 mm). All the solvents were thoroughly dried before use.

Compounds 2a−b. Ameba resin (5.00 g, 6.25 mmol, 1.25 mmol/g) was taken in two reaction vessels. Each part of the resin was swollen in 50 mL of 1% HOAc/DMF and subsequently treated with 5.30 g (25 mmol) of sodium triacetoxyborohydride. To vessel no. 1, 4.00 g (24.0 mmol) of (*R*)-(−)-2-phenylglycine methyl ester and to vessel no. 2, 4.75 g (24.0 mmol) of (*R*)-(−)-2-(*o*-chlorophenyl)glycine methyl ester were added. Both reaction mixtures were stirred at room temperature for 12 h. After the completion of the reaction, the resin was filtered and washed with DMF (3 × 30 mL), methanol (3 × 30 mL), and CH_2Cl_2 (3 × 30 mL) and dried in vacuo for 3 h. A small portion of the resin was then checked by means of the 2,4-dinitrophenylhydrazide test.[24] The absence of red color indicated that the reaction was completed.

Compounds 3a−t. Resins **2a** and **2b** from the previous step were split into 11 and 9 portions, respectively, and poured into the reaction vessels (500.0 mg, 0.625 mmol). The resins were suspended in 7 mL of CH_2Cl_2 and treated with *N*,*N*-diisopropylethylamine (1.30 mL, 7.46 mmol, 12 equiv). Each portion of the compounds **2a−b** was then treated separately with the following carboxylic acid chlorides: *p*-methoxybenzoyl chloride (0.92 mL, 6.25 mmol), *p*-methylbenzoyl chloride (0.90 mL, 6.25 mmol), benzoyl chloride (0.72 mL, 6.25 mmol), *p*-pentylbenzoyl chloride (1.27 mL, 6.25 mmol), *p*-propylbenzoyl chloride (1.03 mL, 6.25 mmol), *p*-fluorobenzoyl chloride (0.82 mL, 6.25 mmol), *p*-chlorobenzoyl chloride (1.09 g, 6.25 mmol), *p*-ethylbenzoyl chloride (1.05 g, 6.25 mmol), nicotinoyl chloride (1.10 g, 6.25 mmol), 2-naphthoyl chloride (1.10 g, 6.25 mmol), and *p*-nitrobenzoyl chloride (1.15 g, 6.25 mmol). The reaction mixtures were stirred at room temperature for 12 h. The resins were filtered and washed with CH_2Cl_2 (3 × 10 mL); methanol (3 × 10 mL); DMF (3 × 10 mL); and finally, with CH_2Cl_2 (3 × 10 mL). The resins were dried in vacuo for 3 h.

Compounds 4a−t. Each of the resin samples from the preceding step was refluxed individually in the presence of 12 mL (1.80 g, 5 equiv) of 15% solution of KOH in 1,4-dioxane/water (3:1) for 3.5 h. After the reaction mixtures were cooled to room temperature, the resins were washed with 1,4-dioxane (3 × 10 mL), water (3 × 10 mL), methanol (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL). The resins were dried in vacuo and checked by means of FT-IR for the absence of the ester carbonyl peak at 1769 cm^{-1} and the presence of the carboxylic acid carbonyl peak at 1730 cm^{-1}, indicating the completion of the reaction.

Compounds 5a−t. The resins from the previous step were swollen individually in 10 mL of CH_2Cl_2 and treated with 1.50 mL of acetic anhydride (14.7 mmol, 23.5 equiv) and 0.30 mL of DEAD (1.87 mmol, 3 equiv) or 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (0.328 g, 1.88 mmol, 3 equiv). The reaction mixtures were stirred at room temperature for 10 h or 5−6 h, respectively. The resins were washed with CH_2Cl_2 (3 × 10 mL); methanol (3 × 10 mL); DMF (3 × 10 mL); and finally, with CH_2Cl_2 (3 × 10 mL) and dried in vacuo for 3 h. The resins were weighed to obtain the mass of each resin before the cleaving step.

General Method for Cleavage of the 3,5-Disubstituted 1,2,4-Triazoles. The polymer-bound 1,2,4-triazoles **5a−t** were treated with 30% TFA/CH_2Cl_2 at room temperature for 1.5 h. The resins were filtered, and the filtrates were evaporated in vacuo to constant weight. The cleavage process was repeated two or three times. The crude products were purified by SiO_2 column chromatography.

3-(4-Methoxyphenyl)-5-phenyl-1*H*-1,2,4-triazole (6a). Yield 92%; white solid, mp 154−156 °C; R_f 0.23 (30% EtOAc/*n*-hexane). IR ν_{max}: 1572, 1648, 2834, 3150 cm^{-1}. ^{1}H NMR (CD_3OD): δ 3.83 (3H, s), 7.02−7.05 (2H, dt, J = 2.4, 9 Hz), 7.46−7.49 (3H, m), 7.95−7.98 (2H, dt, J = 2.4, 9 Hz), 8.04−8.06 (2H, m). ^{13}C NMR (CD_3OD): δ 56.0, 115.5, 115.6, 127.7, 129.3, 129.4, 130.1, 130.6, 131.1, 131.4, 162.9. GC/MS: *m*/*z* 251 (M^+), t_{ret} 8.36 min.

3-(4-Methylphenyl)-5-phenyl-1*H*-1,2,4-triazole (6b). Yield 91%; white solid, mp 180−183 °C (lit.[19] 156−158 °C); R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1587, 1613, 2819, 3141 cm^{-1}. ^{1}H NMR (CD_3OD): δ 2.41 (3H, s), 7.31−7.35 (2H, dt, J = 2.1, 8.4 Hz), 7.48−7.51 (3H, m), 7.92−7.95 (2H, dt, J = 2.1, 8.4 Hz), 8.04−8.07 (2H, dd, J = 1.5, 7.7 Hz). ^{13}C NMR (CD_3OD): δ 21.5, 127.7, 130.1, 130.7, 113.1. GC/MS *m*/*z* 235 (M^+), t_{ret} 7.55 min.

3,5-Diphenyl-1,2,4-triazole (6c). Yield 90%; white solid, mp 190−192 °C (lit.[19] 189−191 °C); R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1561, 1613, 2852, 3132 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.48−7.52 (6H, m), 8.05−8.08 (4H, m). ^{13}C NMR (CD_3OD): δ 127.7, 130.1, 131.2. GC/MS *m*/*z* 221 (M^+), t_{ret} 7.09 min.

3-(4-Pentylphenyl)-5-phenyl-1*H*-1,2,4-triazole (6d). Yield 93%; white solid, mp 143−145 °C; R_f 0.38 (30% EtOAc/*n*-hexane). IR ν_{max}: 1636, 1648, 2892, 3148 cm^{-1}. ^{1}H NMR (CD_3OD): δ 0.88−0.93 (3H, t, J = 6.9 Hz), 1.31−1.40 (4H, m), 1.61−1.71 (2H, m), 2.64−2.69 (2H, t, J = 8.1 Hz), 7.31−7.34 (2H, d, J = 8.4 Hz), 7.48−7.52 (3H, m), 7.94−7.97 (2H, d, J = 8.4 Hz), 8.04−8.08 (2H, dd, J = 1.5, 7.5 Hz). ^{13}C NMR (CD_3OD): δ 14.5, 23.7, 32.3, 32.7, 36.8, 127.7, 127.7, 130.1, 130.1, 131.1. GC/MS: *m*/*z* 291 (M^+), t_{ret} 9.29 min.

3-(4-Propylphenyl)-5-phenyl-1*H*-1,2,4-triazole (6e). Yield 91%; white solid, mp 120−123 °C; R_f 0.36 (30% EtOAc/*n*-hexane). IR ν_{max}: 1543, 1674, 2817, 3146 cm^{-1}. ^{1}H NMR (CD_3OD): δ 0.92−0.97 (3H, t, J = 7.5 Hz), 1.60−1.73 (2H, m), 2.62−2.67 (2H, t, J = 7.7 Hz), 7.32−7.36 (2H, dt, J = 2.1, 8.4 Hz), 7.49−7.54 (3H, m), 7.92−7.96 (2H, dt, J = 2.1, 8.4 Hz), 8.03−8.06 (2H, m). ^{13}C NMR (CD_3OD): δ 14.19, 25.62, 39.0. 125.6, 127.9, 127.9, 128.8, 130.2, 130.4, 131.9, 147.5, 159.0, 159.4, 160.5, 161.1. GC/MS: *m*/*z* 263 (M^+), t_{ret} 8.65 min.

3-(4-Fluorophenyl)-5-phenyl-1*H*-1,2,4-triazole (6f). Yield 90%; yellowish solid, mp 208−211 °C; R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1558, 1627, 2888, 3138 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.16−7.24 (2H, m), 7.45−7.50 (3H, m), 7.98−8.09 (4H, m). ^{13}C NMR (CD_3OD): δ 126.7, 126.7, 127.7, 129.5, 129.8, 130.1, 130.2, 131.5, 159.8, 159.9, 163.7, 167.0 (J_{CF} = 247 Hz). GC/MS: *m*/*z* 239 (M^+), t_{ret} 7.07 min.

3-(3-Pyridyl)-5-phenyl-1*H*-1,2,4-triazole (6g). Yield 93%; white solid, mp 210−213 °C; R_f 0.25 (EtOAc). IR ν_{max}: 1247, 1510, 1641, 2888, 3118 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.50−7.58 (4H, m), 8.07−8.10 (2H, m), 8.38−8.42 (1H, m), 8.65−8.67 (1H, m), 9.25−9.26 (1H, t, J = 1 Hz). ^{13}C NMR (DMSO-d_6): δ 123.9, 126.1, 128.1, 129.0, 130.0, 133.3, 147.0, 150.2, 157.1, 157.2. GC/MS: *m*/*z* 222 (M^+), t_{ret} 7.68 min.

3-Naphthyl-5-phenyl-1*H*-1,2,4-triazole (6h). Yield 95%; white solid, mp 216−218 °C; R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1572, 1622, 2892, 3120 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.49−7.58 (5H, m), 7.90−8.00 (3H, m), 8.08−8.18 (3H, m), 8.59 (1H, brs). ^{13}C NMR (CD_3OD): δ 124.8, 127.3, 127.7, 127.9, 128.3, 129.0, 129.4, 129.7, 129.8, 130.1, 131.3, 134.1, 134.8, 135.6. GC/MS: *m*/*z* 271 (M^+), t_{ret} 10.83 min.

3-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,4-triazole (6i). Yield 83%; white solid, mp 160−163 °C (lit.[27] 134−236 °C); R_f 0.31 (30% EtOAc/*n*-hexane). IR ν_{max}: 1547, 1689, 2873, 3135 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.39−7.57 (4H, m), 8.07−8.14 (2H, m), 8.30−8.40 (3H, m). ^{13}C NMR (DMSO-d_6): δ 123.4, 124.2, 126.2, 126.9, 128.3, 128.3, 128.6, 129.1, 129.3, 135.7. GC/MS: *m*/*z* 266 (M^+), t_{ret} 9.92 min.

3-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,4-triazole (6j). Yield 90%; white solid, mp 222−225 °C (lit.[19] 213-216 °C); R_f 0.35 (30% EtOAc/*n*-hexane). IR ν_{max}: 1584, 1674, 2893, 3153 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.51−7.53 (5H, m), 8.04−8.08 (4H, m). ^{13}C NMR (CD_3OD): δ 124.7, 127.7, 128.3, 129.2, 129.8, 129.8, 130.0, 130.2, 130.5, 131.4. GC/MS: *m*/*z* 255 (M^+), t_{ret} 8.00 min.

3-(4-Ethylphenyl)-5-phenyl-1*H*-1,2,4-triazole (6k). Yield 92%; white solid, mp 170−173 °C; R_f 0.33 (30% EtOAc/*n*-hexane). IR ν_{max}: 1574, 1661, 2910, 3146 cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.23−1.28 (3H, t, J = 7.5 Hz), 2.66−2.73 (2H, q, J = 7.8 Hz), 7.32−7.35 (2H, d, J = 7.8 Hz), 7.46−7.51 (3H, m), 7.94−7.97 (2H, d, J = 8.1 Hz), 8.04−8.07 (2H, m). ^{13}C NMR (CD_3OD): δ 16.0, 29.8, 127.7, 127.8, 129.3, 129.3, 123.6, 129.8, 130.0, 131.1, 134.1, 148.0. GC/MS: *m*/*z* 249 (M^+), t_{ret} 7.87 min.

3-(2-Chlorophenyl)-5-(4-methylphenyl)-1*H*-1,2,4-triazole (6l). Yield 85%; white solid, mp 137−140 °C; R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1579, 1705, 2886, 3128 cm^{-1}. ^{1}H NMR (CD_3OD): δ 2.39 (3H, s), 7.26−7.33 (2H, m), 7.44−7.50 (3H, m), 7.75−7.80 (1H, m), 7.91−7.94 (2H, d, J = 7.8 Hz). ^{13}C NMR (CD_3OD): δ 21.5, 127.7, 128.3, 128.6, 128.8, 129.5, 130.2, 130.7, 131.0, 131.2, 131.5, 132.8, 134.2. GC/MS: *m*/*z* 269 (M^+), t_{ret} 7.99 min.

3-(2-Chlorophenyl)-5-(4-ethylphenyl)-1*H*-1,2,4-triazole (6m). Yield 95%; white solid, mp 143−145 °C; R_f 0.31 (30% EtOAc/*n*-hexane). IR ν_{max}: 1582, 1653, 2885, 3148 cm^{-1}. ^{1}H NMR (CD_3OD): δ 1.25−1.30 (3H, t, J = 7.8 Hz), 2.68−2.75 (2H, q, J = 7.5 Hz), 7.34−7.37 (2H, d, J = 8.4 Hz), 7.43−7.53 (2H, m), 7.57−7.60 (1H, m), 7.76−7.79 (1H, m), 7.94−7.97 (2H, d, J = 8.1 Hz). ^{13}C NMR (CD_3OD): δ 16.1, 29.8, 127.8, 128.3, 129.3, 129.6, 131.5, 132.5, 132.9, 134.3, 134.4, 136.1, 148.2. GC/MS: *m*/*z* 283 (M^+), t_{ret} 8.59 min.

3-(2-Chlorophenyl)-5-(3-pyridyl)-1*H*-1,2,4-triazole (6n). Yield 90%; white solid, mp 180−183 °C; R_f 0.25 (EtOAc). IR ν_{max}: 1522, 1691, 2899, 3159 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.48−7.63 (4H, m), 7.83−7.87 (1H, m), 8.48−8.52 (1H, m), 8.61−8.63 (1H, m), 9.26−9.27 (1H, d, J = 1 Hz). ^{13}C NMR (CD_3OD): δ 125.6, 128.6, 131.6, 132.9, 133.0, 134.0, 135.8, 148.2, 151.0. GC/MS: *m*/*z* 256 (M^+), t_{ret} 7.62 min.

3-(2-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-1,2,4-triazole (6o). Yield 89%; white solid, mp 173−175 °C; R_f 0.33 (30% EtOAc/*n*-hexane). IR ν_{max}: 1545, 1657, 2893, 3152 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.21−7.28 (2H, m), 7.44−7.54 (2H, m), 7.58−7.61 (1H, m), 7.78−7.81 (1H, m), 8.07−

8.12 (2H, m). ^{13}C NMR (CD_3OD): δ 116.8, 117.1, 128.4, 129.8, 129.9, 131.6, 132.7, 132.8, 134.1, 163.7, 167.02 (J_{CF} = 247 Hz). GC/MS: *m*/*z* 273 (M^+), t_{ret} 11.21 min.

3-(2-Chlorophenyl)-5-(4-nitrophenyl)-1*H*-1,2,4-triazole (6p). Yield 85%; white solid, mp 250−253 °C; R_f 0.29 (30% EtOAc/*n*-hexane). IR ν_{max}: 1560, 1668, 2887, 3135 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.50−7.60 (2H, m), 7.65−7.69 (1H, m), 7.86−7.89 (1H, dd, J = 2.1, 7.2 Hz), 8.30−8.40 (4H, m). ^{13}C NMR (DMSO-d_6): δ 124.35, 127.0, 127.5, 130.4, 131.6, 131.7. GC/MS: *m*/*z* 300 (M^+), t_{ret} 9.41 min.

3-(2-Chlorophenyl)-5-(4-propylphenyl)-1*H*-1,2,4-triazole (6q). Yield 92%; white solid, mp 126−128 °C; R_f 0.32 (30% EtOAc/*n*-hexane). IR ν_{max}: 1578, 1668, 2892, 3143 cm^{-1}. ^{1}H NMR (CD_3OD): δ 0.94−0.99 (3H, t, J = 7.5 Hz), 1.68−1.72 (2H, m), 2.63−2.68 (2H, t, J = 8.1 Hz), 7.31−7.34 (2H, d, J = 8.1 Hz), 7.42−7.52 (2H, m), 7.57−7.60 (1H, m), 7.76−7.79 (1H, dd, J = 2.1, 7.2 Hz), 7.94−7.96 (2H, d, J = 8.4 Hz). ^{13}C NMR (CD_3OD): δ 14.2, 25.7, 39.0, 127.7, 128.3, 129.6, 130.2, 131.5, 132.4, 132.9, 134.3. GC/MS: *m*/*z* 297 (M^+), t_{ret} 8.65 min.

3-(2-Chlorophenyl)-5-(4-chlorophenyl)-1*H*-1,2,4-triazole (6r). Yield 91%; white solid, mp 191−195 °C; R_f 0.34 (30% EtOAc/*n*-hexane). IR ν_{max}: 1588, 1689, 2884, 3146 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.36−7.66 (5H, m), 7.73−7.87 (1H, m), 7.98−8.14 (2H, m). ^{13}C NMR (CD_3OD): δ 128.5, 129.2, 129.8, 130.2, 130.5, 130.8, 131.1, 131.6, 132.8, 132.9, 134.1, 137.0. GC/MS: *m*/*z* 289 (M^+), t_{ret} 7.90 min.

3-(2-Chlorophenyl)-5-(4-methoxyphenyl)-1*H*-1,2,4-triazole (6s). Yield 87%; yellowish solid, mp 145−147 °C; R_f 0.30 (30% EtOAc/*n*-hexane). IR ν_{max}: 1563, 1689, 2889, 3129 cm^{-1}. ^{1}H NMR (CD_3OD): δ 3.85 (3H, s), 7.03−7.08 (2H, m), 7.43−7.52 (2H, m), 7.56−7.60 (1H, m), 7.75−7.78 (1H, m), 7.95−8.00 (2H, m). ^{13}C NMR (CD_3OD): δ 56.0, 122.2, 128.3, 128.6, 129.3, 130.7, 131.1, 131.2, 131.5, 132.4, 132.8, 134.3, 162.9. GC/MS: *m*/*z* 285 (M^+), t_{ret} 9.85 min.

3-(2-Chlorophenyl)-5-(2-naphthyl)-1*H*-1,2,4-triazole (6t). Yield 96%; white solid, mp 180−183 °C; R_f: 0.31 (30% EtOAc/*n*-hexane). IR ν_{max}: 1588, 1635, 2892, 3114 cm^{-1}. ^{1}H NMR (CD_3OD): δ 7.49−7.63 (5H, m), 7.82−7.86 (1H, dd, J = 2.4, 7.5 Hz), 7.91−8.01 (3H, m), 8.14−8.17 (1H, d, J = 8.4 Hz), 8.59 (1H, brs). ^{13}C NMR (CD_3OD): δ 124.8, 127.3, 128.0, 128.4, 129.0, 129.4, 129.7, 129.9, 130.2, 130.8, 131.1, 131.3, 131.6, 132.7, 132.9, 134.2, 134.8, 135.6. GC/MS: *m*/*z* 305 (M^+), t_{ret} 10.66 min.

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