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An Improved Synthesis of 1,2,4-Triazoles using Ag_2CO_3

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Abstract—An improved synthesis of 1,3,5-trisubstituted 1,2,4-triazoles via Ag_2CO_3 mediated cyclization of triazenes has been developed. This approach is flexible and compatible with a wide range of functional groups. The reaction was complete within 3 h and the products were isolated in moderate to high yields. The influence of the β-substituents of the amines on the triazole formation was also studied.

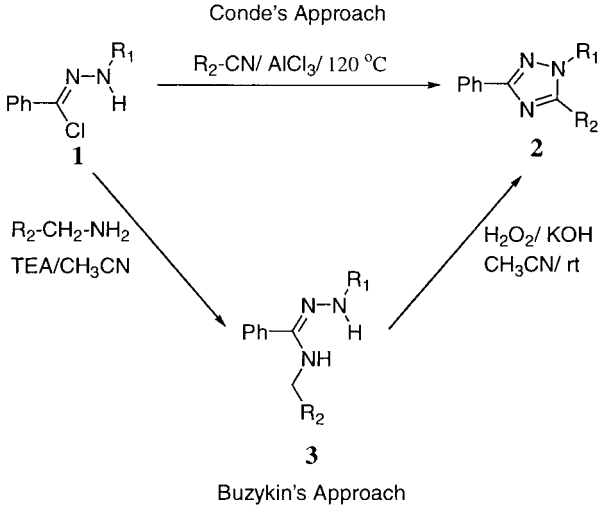
Introduction

Compounds with 1,2,4-triazole moiety have received considerable attention among medicinal chemists because molecules with these structural features have been found to display a wide range of potent biological activities, such as antihypertensive,[1] antifungal[2] and antibacterial[3] activities. Appropriately functionalized 1,2,4-triazoles, such as 4-[3,5-bis (2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic acid, have been shown to selectively form a complex with iron(III), which is useful in iron overload therapy.[4] Considering the important biological properties of 1,2,4-triazole compounds, several efficient triazole syntheses have been reported.[5]

Most of the previously reported triazole syntheses made use of the hydrazonyl chloride **1**, readily prepared in a single step from the corresponding hydrazone, as a common synthetic intermediate. Conde and co-workers prepared triazole by heating a mixture of the hydrazonyl chloride **1** and aromatic or aliphatic nitrile in *o*-dichlorobenzene at 120–130°C in the presence of one equiv of $AlCl_3$ (Scheme 1).[5a] The triazole **2** is formed via a 1,3-dipolar cycloaddition of nitrilimine, generated in situ from **1** and $AlCl_3$, to nitrile. Instead of $AlCl_3$, triethylamine (TEA)[6] and Ag_2CO_3[7] have also been used to generate the nitrilimine intermediate. In an alternative two-step approach, Buzykin et al. first prepared a triazene intermediate **3** from the reaction of **1** with a primary amine and TEA, which was then treated with a solution of 30% hydrogen peroxide/ aqueous KOH to yield the triazole **2** in moderate yield (Scheme 1).[5e,5f] In this route, the triazole is believed to form via an azoimine formation, tautomerization, cyclization and oxidation.[5f] Commercial availability of a large selection of primary amines and the mild reaction condition make the Buzykin's approach synthetically very attractive. Despite the mild reaction conditions, to the best of our knowledge, the synthetic scope and the functional group tolerance of this reaction have not been fully exploited. As part of our efforts directed toward the identification of novel biologically active compounds from combinatorial libraries of small molecules, we became interested in investigating the synthetic scope of the Buzykin's triazole synthesis. In this paper we report our findings on this study and also disclose an efficient Ag_2CO_3 mediated 1,2,4-triazole synthesis.

Results and Discussion

Our study began with the preparation of the hydrazonyl chloride **7a** (Scheme 2). Condensation of benzaldehyde (**4**) and phenylhydrazine (**5a**) in benzene gave the hydrazone



Scheme 1. Preparation of triazole.

Keywords: hydrazone; nitrilimines; cycloaddition; triazoles.

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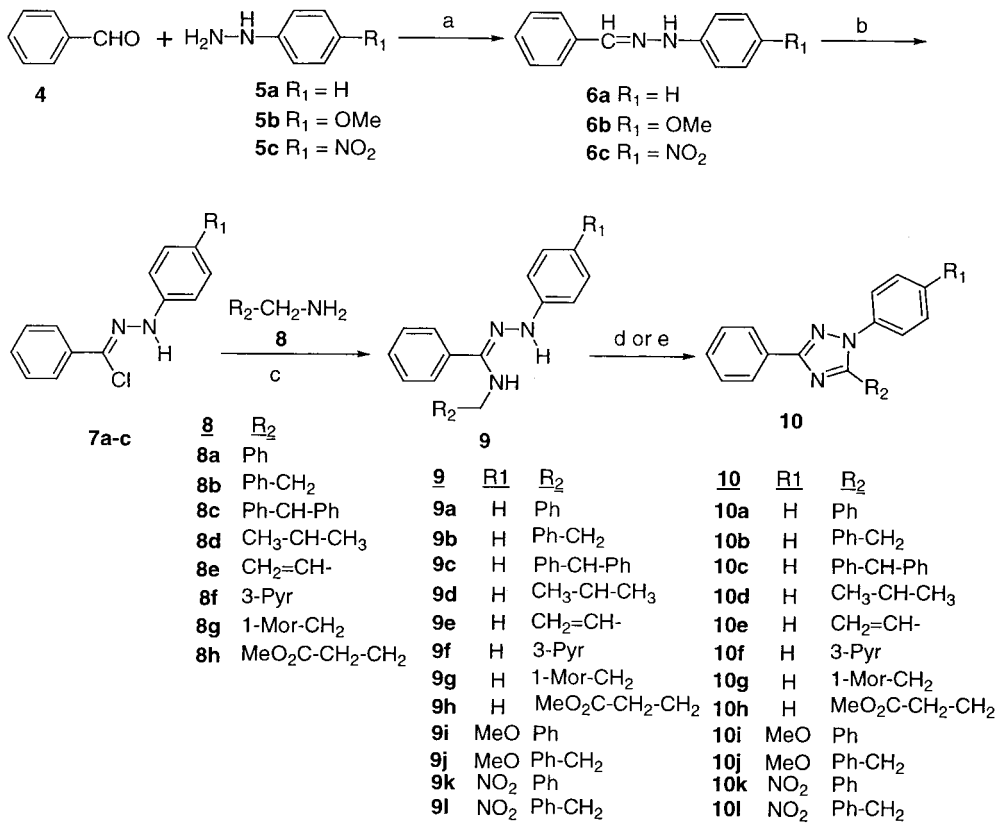
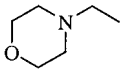


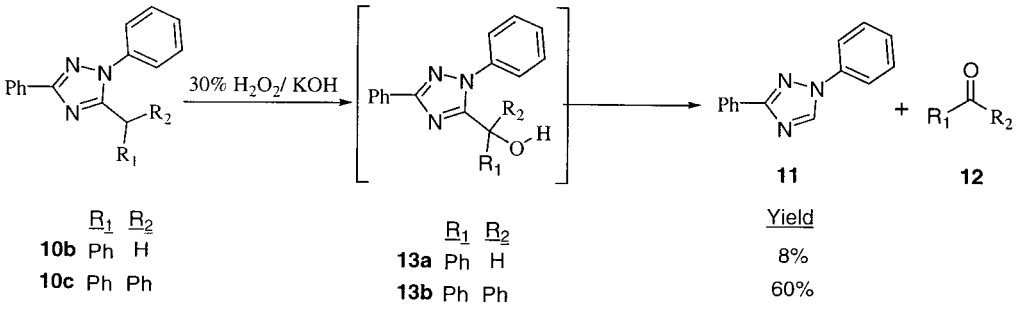
Scheme 2. (a) Benzene, rt, 12 h; (b) 1.5 equiv. of NCS, 3 equiv. of DMS, CH_2Cl_2 0°C to −78°C to rt; (c) 1.1 equiv. of **8**, 1.1 or 2.2 equiv. of TEA, CH_3CN, rt; 12 h; (d) 30% H_2O_2/sat KOH (90:10 v/v), CH_3CN, 0°C to rt; (e) 1.2 equiv. of Ag_2CO_3, CH_3CN, 2 h.

6a. After removal of the solvent, the hydrazone **6a** was taken in CH_2Cl_2 and allowed to react with a *N*-chlorosuccinimide (NCS)/dimethyl sulfide (DMS) complex under Patel's reaction conditions[8] with slight modification to furnish the hydrazonyl chloride **7a** in 69% yield (for two steps) after chromatographic purification. The hydrazonyl chloride **7a** was then subjected to triazole formation following Buzykin's procedure.[5f] Accordingly, reaction of **7a** with

Table 1. Preparation of triazoles

Entry	Compound	R_1	R_2		Yield %[a]
1	**10a**	H	Ph–	**8a**	69 (16)[b]
2	**10b**	H	Ph–CH_2–	**8b**	62 (8)[b]
3	**10c**	H		**8c**	5 (6)[b]
4	**10d**	H		**8d**	40
5	**10e**	H	CH_2=CH–	**8e**	51
6	**10f**	H		**8f**	47
7	**10g**	H		**8g**	37
8	**10h**	H	MeO_2C–CH_2–CH_2–	**8h**	73
9	**10i**	OMe	Ph–	**8a**	66
10	**10j**	OMe	Ph–CH_2–	**8b**	48
11	**10k**	NO_2	Ph–	**8a**	78
12	**101**	NO_2	Ph–CH_2–	**8b**	60

[a] Overall yield for two steps **7**.
[b] H_2O_2/KOH method.



	R_1	R_2
10b	Ph	H
10c	Ph	Ph

	R_1	R_2
13a	Ph	H
13b	Ph	Ph

Scheme 3. Formation of 1,3-disubstituted triazoles.

1.1 equiv. of benzylamine (**8a**) and 1.1 equiv. of triethylamine (TEA) in acetonitrile for 24 h provided the triazene **9a**. Without purification, the crude triazene **9a** in acetonitrile was treated with a solution of aqueous KOH (5–10% v/v)/30% H_2O_2 to yield the corresponding triazole **10a** in 16% overall yield from **7a**, after column chromatography (Table 1, entry 1). It should be noted that after the addition of KOH/H_2O_2 mixture the reaction becomes vigorous and additional precaution should be taken to avoid any overflow or spill by performing the reaction in a bigger reaction flask at lower temperature (<0°C). To our disappointment, under similar reaction conditions, 2-phenylethylamine (**8b**) and 2,2-diphenylethylamine (**8c**) yielded the corresponding triazoles **10b** and **10c** in 8 and 6% yields, respectively (Scheme 2, Table 1, entries 2 and 3). Isolation of **10b** and **10c** in low yields was mainly due to the formation of unidentified side products. One of the identified side products was 1,3-disubstituted 1,2,4-triazole **11** (Scheme 3). In the case of amine **8c**, in addition to **10c** and **11**, benzophenone (**12**) was also isolated. Furthermore, when the triazene **9c** and KOH/H_2O_2 were allowed to react for a longer time (>24 h) the side product **11** was isolated as the major product and no desired triazole **10c** was observed. When benzylamine (**8a**) was used no side product **11** was detected. The isolation of the side products **11** and **12** could be explained via a two-step, one-pot reaction sequence (Scheme 3). The first step involves the introduction of a hydroxyl group at the α-methylene/methine carbon to give an alcohol intermediate **13** which immediately undergoes a base promoted fragmentation to yield the undesired side products **11** and **12**. However, no further mechanistic study was carried out to confirm this proposed mechanism. Investigation of the reaction with a range of primary amines indicated that the nature of the substituent on the β-position of the amine **8** had a significant impact on the yield of **11** (Scheme 3, R_1=R_2=Ph 60% yield; R_1=Ph, R_2=H 6% yield). Isolation of **11** in moderate yield (60%) from **7a** and **8c** suggests that this approach can be used as an alternative to the existing routes to prepare 1,3-disubstituted 1,2,4-triazoles. In addition to side products formation, building blocks with carbon–carbon double bond, thioether, tertiary amine and ester functionalities could not be used under the KOH/H_2O_2 conditions because they were susceptible to either oxidation or hydrolysis. Limited functional group compatibility and isolation of triazoles in low yields made Buzykin's approach unsuitable for combinatorial library preparation. These limitations led us to examine an alternative reaction condition that would tolerate a wide range of funtionalities and provide triazoles in synthetically useful yield.

Based on the above results, we reasoned that replacing the KOH/H_2O_2 mixture with a milder reagent would make this approach compatible with more functionalities and suppress the side product formation. We began our investigation by treating the triazene **9a** with various organic and inorganic reagents, such as TEA, DIEA, KF, $NaHCO_3$, Cs_2CO_3, K_2CO_3 and Ag_2CO_3. Accordingly, the triazene **9a** in CH_3CN was treated with 1.5 equiv. of the reagent and the reaction progress was monitored by thin layer chromatography (TLC) and LC/MS. Among all the reagents examined, Ag_2CO_3 smoothly promoted the cyclization and provided the triazole **10a** in 69% yield over the two steps from **7a** (Scheme 2, Table 1, entry 1). The reaction was very clean and complete within 3 h. In the absence of Ag_2CO_3, only a trace of the triazole **10a** was observed, indicating that Ag_2CO_3 was necessary to convert the triazene **9a** into triazole **10a**. Presumably, the oxidizing property of Ag_2CO_3 may have contributed in the cyclization of the triazene **9a** to the triazole **10a** via an azoimine formation, tautomerization, cyclization and oxidation, as proposed by Buzykin.[5f] To the best of our knowledge, this is the first example of silver carbonate promoted synthesis of triazole from triazene. In addition to promoting the triazole formation under mild reaction condition, use of solid Ag_2CO_3 simplifies the work-up procedure by eliminating the aqueous work-up. Removal of CH_3CN followed by purification of the crude mixture provided the triazole **10a**.

In order to examine the synthetic scope and the functional group tolerance of the Ag_2CO_3 mediated synthesis, the reaction sequence was studied with a variety of primary amines **8b–h** and hydrazines **5b**,**c** (Table 1, entries 2–12). Treatment of amines **8b–h** with hydrazonyl chloride **7a** provided the corresponding triazenes **9b–h**, which were then treated with Ag_2CO_3 to give the desired triazoles **10b–h** (Table 1 entries 2–8). As shown in Table 1, in most of the cases, the desired triazoles were isolated in synthetically useful yields. The amines **8b** and **8c** provided the corresponding triazoles **10b** and **10c** in 62% and 5% yields, respectively. To our disappointment, use of Ag_2CO_3 failed to improve the yield of **10c** and the side product **11** was isolated as the major product (>60%). No further optimization study was carried out to suppress the side product **11** formation. In the case of amines **8f** and **8g**, the corresponding triazoles **10f** and **10g** were isolated in moderate yields without any *N*-oxide formation, whereas Buzykin's KOH/H_2O_2 route yielded the corresponding *N*-oxides along with **10f** and **10g**. The ester and vinyl functionalities present in the triazoles **10e** and **10h**, respectively, could be used as handles to introduce additional structural diversity.

Given the success in isolating the triazoles in moderate yields, we then examined the influence of electronically different hydrazines on the triazole formation. The hydrazonyl chlorides **7b**[9] and **7c**, prepared from 4-methoxy and 4-nitrophenylhydrazine (**5b**) and (**5c**), respectively, were subjected to the triazole synthesis with amines **8a** and **8b**. Under the above reaction conditions, the cyclization proceeded smoothly and yielded the corresponding triazoles **10i–l** in moderate yields (Scheme 2, Table 1, entries 9–12), indicating that the electronic effect did not have any major impact on the triazole formation.

Conclusion

We have described an improved synthesis of 1,3,5-trisubstituted 1,2,4-triazoles via Ag_2CO_3 mediated cyclization of triazene. The reaction was fast and, in most cases, the triazoles were isolated in synthetically useful yields. The impact of the β-substituent of the amine on the yield of the triazole has been studied. This approach is compatible with a wide range of functional groups, which is a valuable advantage over the previously reported method. Commercial availability of a diverse collection of primary amines and aldehydes makes this route suitable for the preparation of large numbers of triazoles. This approach is also amenable to scale-up. We are currently optimizing the triazole synthesis on solid support and the results will be published in due course.

Experimental

General methods

All solvents and reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectral data were obtained on a Varian Gemini 400 instrument with the solvents noted. Chemical shifts were reported in the δ scale in ppm relative to TMS (0.00 ppm) as internal standard. ^{13}C NMR spectra were obtained by using the above instrument operating at 100 MHz with solvents noted.

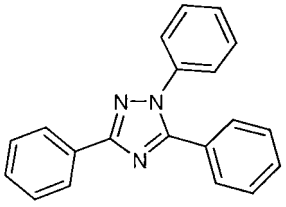
General procedure for the preparation of hydrazonyl chloride 7a–c

To a solution of benzaldehyde (**4**) (1.0 g, 9.43 mmol, 1.0 equiv.) in benzene (40 mL) was added hydrazine **5** (9.43 mmol, 1.0 equiv.) and the reaction mixture was stirred at rt for 12 h. Removal of the solvent provided the crude hydrazone **6**, which was used in the next step without further purification. To a solution of NCS (1.89 g, 14.15 mmol, 1.5 equiv.) in CH_2Cl_2 (25 mL) at 0°C was added dimethylsulfide (1.76 g, 28.29 mmol, 3.0 equiv.) and the reaction mixture was stirred for 15 min at this temperature and then cooled to −78°C. To this solution was added the hydrazone **6** (9.43 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) and the reaction mixture was stirred for 1 h at this temperature and then allowed to warm to rt and stirred at rt for 2 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc 98:2 to 90:10) to afford the hydrazonyl chloride **7**.

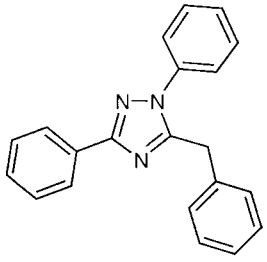
General procedure for the preparation of triazoles 10a–l

Ag_2CO_3 method. To a solution of hydrazonyl chloride **7** (1.64 mmol, 1.0 equiv.) in CH_3CN (8 mL) were added amine **8** (1.1 equiv.) and TEA (1.1 equiv.; 2.2 equiv. for amine **8h**) and the reaction mixture was stirred at rt for 12 h to yield the triazene **9** (1.64 mmol). After removal of the solvent, the crude **9** was taken in fresh CH_3CN (8 mL) and Ag_2CO_3 (0.68 g, 2.46 mmol, 1.5 equiv.) was added and the reaction mixture was stirred at room temperature for 2–3 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc) to provide triazole **10**.

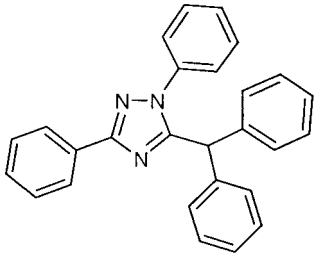
KOH/H_2O_2 method. To a solution of crude triazene **9** (1.64 mmol) in CH_3CN (7 mL) at 0°C was added 7 mL of a (90:10 v/v) mixture of 30% H_2O_2 and sat. KOH (5 g in 10 mL of H_2O) and the reaction mixture was stirred at rt until disappearance of the triazene **9**. The reaction mixture was then diluted with EtOAc and washed with water. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/EtOAc) to afford triazole **10**.



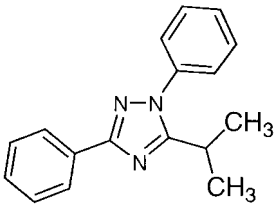
Compound 10a. IR (neat): ν_{max} 3383, 1493, 1474, 1440, 1394, 1341 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.34–7.50 (m, 11H), 7.54–7.58 (m, 2H), 8.22–8.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 125.5, 126.7, 128.1, 128.7, 128.9, 129.1, 129.5, 130.1, 130.9, 138.4, 154.9, 162.1; HRMS (FAB) calcd for $C_{20}H_{16}N_3$ (M+H) 298.1344, found 298.1350.



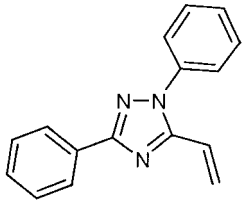
Compound 10b. Mp 83–84°C; IR (neat): ν_{max} 3377, 3056, 3025, 1595, 1501, 1448, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.23 (s, 2H), 7.16–7.18 (m, 2H), 7.22–7.29 (m, 3H), 7.36–7.38 (m, 2H), 7.41–7.48 (m, 6H), 8.17–8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 32.7, 125.5, 126.7, 127.1, 128.6, 128.7, 128.8, 129.2, 129.4, 129.5, 131.0, 136.1, 137.5, 155.1, 161.8; HRMS (FAB) calcd for $C_{21}H_{18}N_3$ (M+H) 312.1501, found 312.1503.



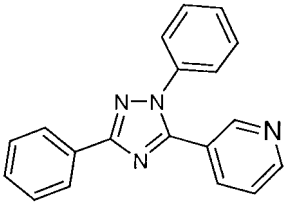
Compound 10c. IR (neat): ν_{max} 3417, 1640, 1494, 1441 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 5.47 (s, 1 H), 7.21–7.49 (m, 18H), 8.17 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 48.4, 126.0, 126.7, 127.2, 128.5, 128.7, 128.9, 129.3, 129.4, 129.5, 131.1, 137.4, 140.5, 157.1, 161.8; HRMS (FAB) calcd for $C_{27}H_{22}N_3$ (M+H) 388.1814, found 388.1910.



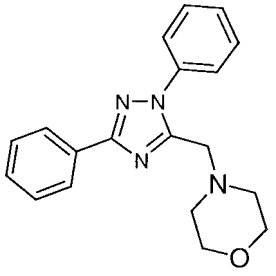
Compound 10d. IR (neat): ν_{max} 3317, 3065, 2966, 2926, 1593, 1501, 1441, 1355, 1109 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.37 (d, J=6.8 Hz, 6H), 3.16 (m, 1H), 7.36–7.57 (m, 8H), 8.14–8.17 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 21.8, 26.0, 125.7, 126.6, 128.6, 129.1, 129.2, 129.5, 131.2, 137.7, 161.5, 162.0; HRMS (FAB) calcd for $C_{17}H_{18}N_3$ (M+H) 264.1501, found 264.1495.



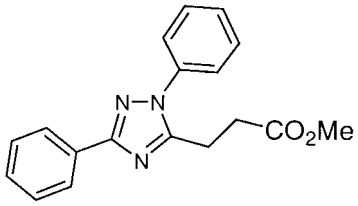
Compound 10e. Mp 75–77°C; IR (neat): ν_{max} 3516, 1640, 1487, 1441, 1341 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.68 (dd, J=10.8, 1.8 Hz, 1H), 6.53 (dd, J=17.4, 1.8 Hz, 1H), 6.64 (dd, J=17.4, 10.8 Hz, 1H), 7.41–7.56 (m, 8H), 8.18–8.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 121.7, 123.8, 125.4, 126.6, 128.6, 129.1, 129.4, 129.5, 130.8, 137.1, 152.9, 161.8; HRMS (FAB) calcd for $C_{16}H_{13}N_3$ (M+H) 248.1188, found 248.1197.



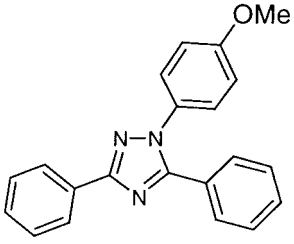
Compound 10f. Mp 124–126°C; IR (neat): ν_{max} 3397, 1646, 1487, 1441, 1408, 1348 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.31 (ddd, J=8.0, 4.8, 0.8 Hz, 1H), 7.39–7.49 (m, 8H), 7.89 (dt, J=7.8, 2.0 Hz, 1H), 8.19–8.23 (m, 2H), 8.63 (dd, J=4.8, 2.0 Hz, 1H), 8.77 (d, J=2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 123.2, 124.3, 125.4, 126.5, 128.6, 129.3, 129.5, 129.6, 130.3, 136.0, 137.7, 149.3, 150.6, 151.9, 162.2; HRMS (FAB) calcd for $C_{19}H_{15}N_4$ (M+H) 299.1297, found 299.1298.



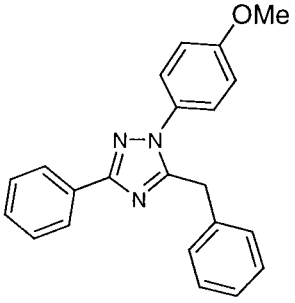
Compound 10g. IR (neat): ν_{max} 3409, 1680, 1494, 1441, 1196, 1123 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 2.61 (t, J=4.8 Hz, 4H), 3.67 (s, 2H), 3.69 (t, J=4.8 Hz, 4H), 7.38–7.53 (m, 6H), 7.72–7.76 (m, 2H), 8.13–8.17 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 53.0, 53.2, 66.8, 124.8, 126.5, 128.6, 128.9, 129.3, 129.4, 130.6, 137.6, 152.0, 161.4; HRMS (FAB) calcd for $C_{19}H_{21}N_4O$ (M+H) 321.1715, found 321.1713.



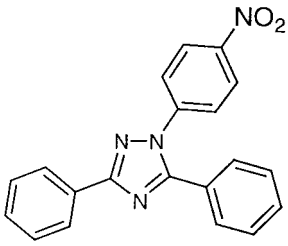
Compound 10h. Mp 78–79°C; IR (neat): ν_{max} 3436, 1733, 1646, 1494, 1434, 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.95 (t, J=7.3 Hz, 2H), 3.12 (t, J=7.3 Hz, 2H), 3.68 (s, 3H), 7.36–7.54 (m, 8H), 8.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 21.9, 31.4, 51.8, 125.0, 126.4, 128.5, 128.9, 129.2, 129.5, 130.9, 137.3, 155.2, 161.3, 172.5; HRMS (FAB) calcd for $C_{18}H_{18}N_3O_2$ (M+H) 308.1399, found 308.1400.



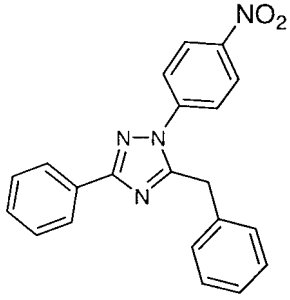
Compound 10i. Mp 95–97°C; IR (neat): ν_{max} 3410, 3059, 2833, 1640, 1507, 1474, 1440, 1288, 1242 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.85 (s, 3H), 6.93 (d, J=8.8 Hz, 2H), 7.31–7.46 (m, 8H), 7.55 (m, 2H), 8.21 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 55.7, 114.7, 126.7, 127.0, 128.2, 128.7, 129.0, 129.5, 130.0, 131.0, 131.5, 154.8, 159.9, 161.8; HRMS (FAB) calcd for $C_{21}H_{18}N_3O$ (M+H) 328.1450, found 328.1452.



Compound 10j. IR (neat): ν_{max} 3377, 2833, 1633, 1514, 1448, 1348, 1249 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.85 (s, 3H), 4.17 (s, 2H), 6.94 (m, 2H), 7.15 (m, 2H), 7.20–7.26 (m, 5H), 7.38–7.46 (m, 3H), 8.15 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 32.6, 55.7, 114.6, 126.6, 127.0, 128.6, 128.7, 128.8, 129.4, 130.4, 131.1, 136.2, 155.3, 160.2, 161.6; HRMS (FAB) calcd for $C_{22}H_{20}N_3O$ (M+H) 342.1606, found 342.1598.



Compound 10k. Mp 162–164°C; IR (neat): ν_{max} 3390, 1600, 1520, 1487, 1441, 1341, 1275 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.39–7.49 (m, 6H), 7.51–7.54 (m, 2H), 7.58–7.62 (m, 2H), 8.18–8.22 (m, 2H), 8.24–8.28 (m, 2H); ^{13}C NMR (DMSO-d_6) δ:124.8, 125.2, 126.7, 127.6, 128.7, 129.0, 129.1, 129.9, 130.1, 130.7, 142.9, 146.8, 155.3, 162.6; HRMS (FAB) calcd for $C_{20}H_{15}N_4O_2$ (M+H) 343.1195, found 343.1197.



Compound 10l. Mp 152–154°C; IR (neat): ν_{max} 3364, 1593, 1527, 1487, 1448, 1348 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 4.33 (s, 2H), 7.18–7.34 (m, 5H), 7.44–7.51 (m, 3H), 7.60–7.64 (m, 2H), 8.18–8.21(m, 2H), 8.30–8.33 (m, 2H); ^{13}C NMR (DMSO-d_6) δ: 33.2, 124.8, 124.9, 126.6, 127.4, 128.3, 128.7, 129.0, 129.8, 130.2, 135.2, 142.3, 147.0, 155.1, 162.3; HRMS (FAB) calcd for $C_{21}H_{17}N_4O_2$ (M+H) 357.1352, found 357.1345.

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9. Treatment of hydrazine **6b** with NCS/DMS, under our modified reaction condition, gave a separable mixture of **7b** and **14**.