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Cyclization of 1,2,4-triazenes to 1,2,4-triazoles using oxidizing reagents—NaClO, $Ca(ClO)_2$, Dess–Martin periodinane and Ley's TPAP/NMO

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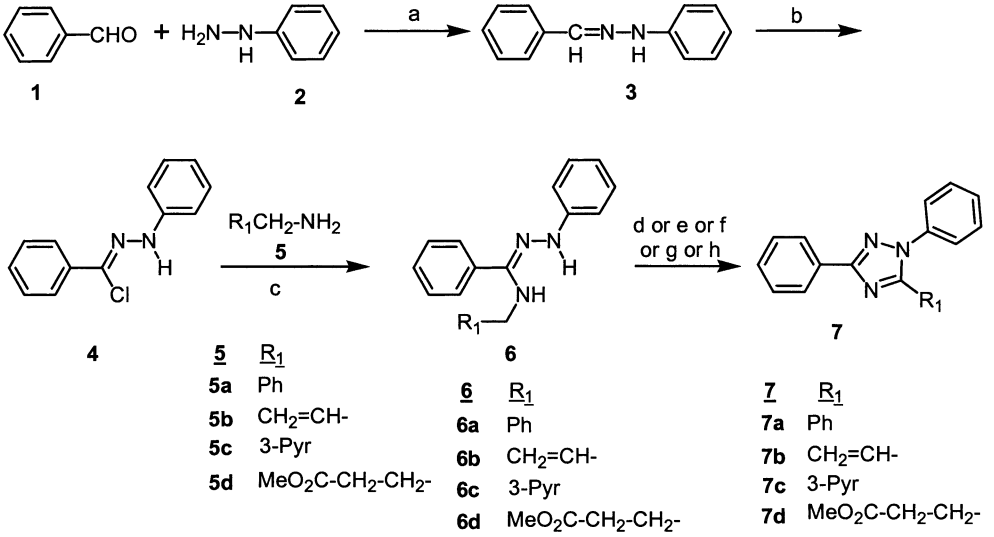
Abstract—A simple and efficient approach to 1,3,5-trisubstituted 1,2,4-triazoles via cyclization of 1,2,4-triazenes employing commonly used oxidizing agents such as NaClO, $Ca(ClO)_2$, Dess–Martin periodinane and Ley's oxidizing agent (TPAP/NMO) is described. The reaction proceeds under mild conditions and is compatible with various functional groups. Extension of this approach to prepare triazoles on solid support has also been investigated. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Compounds containing 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] Buzykin et al. reported a simple approach to 1,2,4-triazole **7** through a H_2O_2 mediated cyclization of triazene **6**.[4] Due to its limited functional group compatibility, this approach could not be used in our medicinal chemistry program to prepare combinatorial libraries of triazoles. After a systematic investigation, we recently reported an improved synthesis of 1,3,5-trisubstituted 1,2,4-triazole **7** via a Ag_2CO_3 mediated cyclization of triazene **6** (Scheme 1).[5] The mild reaction conditions and tolerance to a wide range of functional



Scheme 1. (a) C_6H_6, room temperature, 12 h; (b) 1.5 equiv. of NCS, 3.0 equiv. of DMS, CH_2Cl_2, 0 to −78°C to room temperature; (c) 1.2 equiv. of **5**, 1.2 equiv. of TEA (2.4 equiv. for **5d**), CH_3CN, room temperature, 15 h; (d) 1.2 equiv. of Ag_2CO_3, CH_3CN, 2 h; (e) NaClO, CH_3CN, 24 h; (f) 2.0 equiv. of $Ca(ClO)_2$, CH_3CN, 24 h; (g) 1.5 equiv. of DMP, CH_2Cl_2, 3 h; (h) 0.2 equiv. of TPAP/1.5 equiv. of NMO, CH_3CN, 3 h.

Keywords: hydrazone; nitrilimines; cycloaddition; triazoles.

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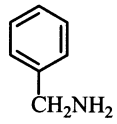
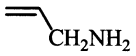
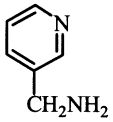
Table 1. Preparation triazoles using various oxidizing agents

Entry	Triazole	$R_1–CH_2–NH_2$	Yield (%)				
			Ag_2CO_3[a]	NaClO	$Ca(ClO)_2$	Dess–Martin periodinane	TPAP/NMO
1	**7a**		69	68	65	81	79
2	**7b**		51	63	51	69	60
3	**7c**		47	45	63	52	45
4	**7d**	$MeO_2C–(CH_2)_3–NH_2$	73	59	73	86	75

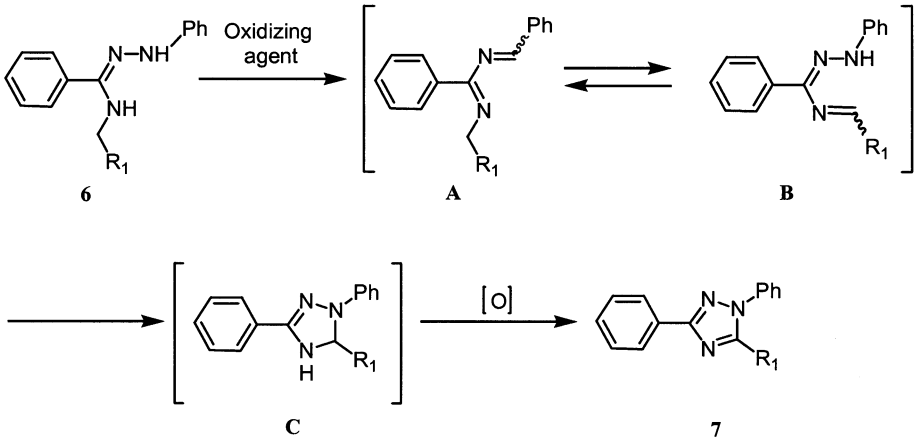
[a] See Ref. 5.

groups make this approach very attractive synthetic route for rapid synthesis of molecules with 1,2,4-triazole skeleton. As part of our efforts directed toward the preparation of combinatorial libraries[6] of small molecules to identify novel biologically active compounds, we became interested in constructing combinatorial libraries of 1,3,5-trisubstituted 1,2,4-triazoles on solid support[7] using our Ag_2CO_3 mediated cyclization approach. Unfortunately, the use of Ag_2CO_3 on solid support made the washing process very difficult and the resin could not be efficiently separated from Ag_2CO_3. In order to eliminate the practical difficulties associated with the use of Ag_2CO_3, we wanted to find alternative reagents that could promote the cyclization of 1,2,4-triazene to 1,2,4-triazole in solution and on solid support. Herein we report the result of this investigation which led to the identification of various oxidizing agents such as NaClO,[8,9] $Ca(ClO)_2$,[10] Dess–Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, DMP)[11] and Ley's oxidizing agent (tetra-*n*-propylammonium perruthenate (VII)/4-methylmorpholine *N*-oxide, TPAP/NMO)[12] to cyclize the triazene **6** to triazole **7**.

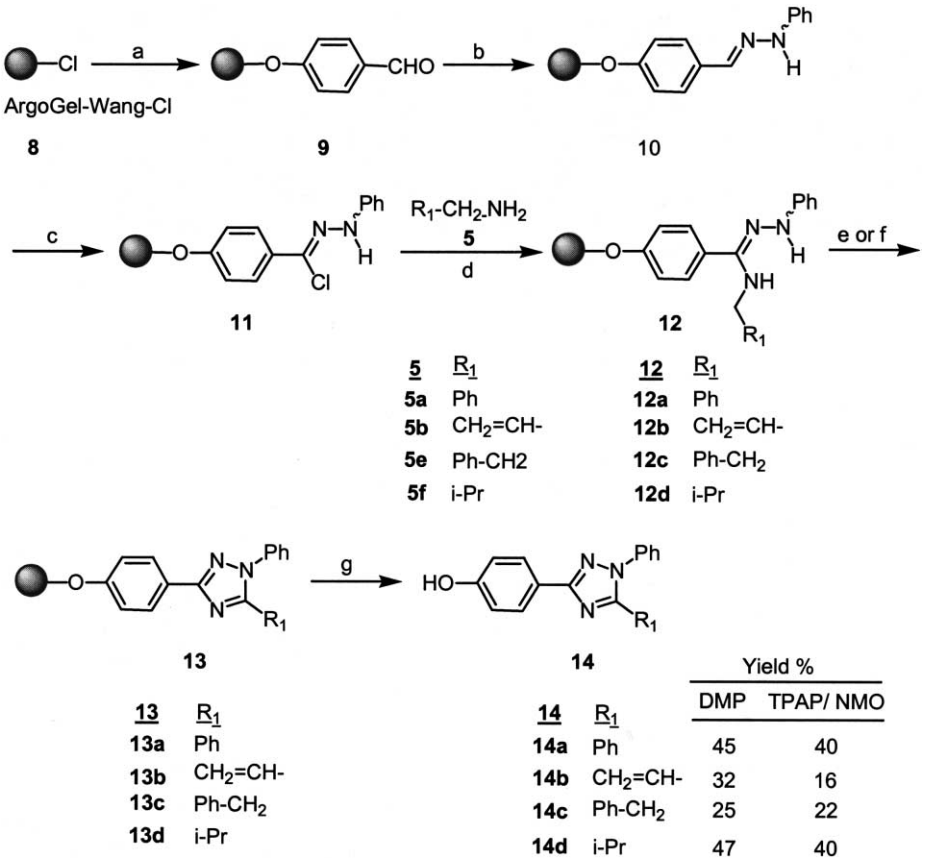
2. Results and discussion

Our initial optimization study was carried out in solution and the triazene **6a** was chosen as the model system to investigate the cyclization reaction. The requisite triazene **6a** was readily prepared using literature procedure.[4,5] Reaction of the hydrazone **3**, prepared from condensation of benzaldehyde (**1**) and phenylhydrazine (**2**), with a *N*-chlorosuccinimide (NCS)/dimethyl sulfide (DMS) complex[13] gave the hydrazonyl chloride **4**. Treatment of **4** with 1.2 equiv. of benzylamine (**5a**) and 1.2 equiv. of triethylamine (TEA) in CH_3CN for 15 h followed by removal of the solvent and excess TEA provided the crude triazene **6a**. The triazene **6a** was then allowed to react with various reagents to promote the cyclization and the reaction progress was monitored by thin layer chromatography (TLC) and LC/MS.

Assuming that the oxidizing property of Ag_2CO_3[14] was responsible for the cyclization of triazene **6a** to triazole **7a**, we speculated that the reaction of triazene **6a** with an oxidizing agent would promote the cyclization to give the triazole **7a**. To test our hypothesis, initially, NaClO solution (sodium hypochlorite, Aldrich) was chosen because it is readily available and has been widely used as an oxidizing agent in organic synthesis.[8,9] As predicted, treatment of triazene **6a** in CH_3CN with NaClO solution for 24 h smoothly promoted the cyclization and yielded the triazole **7a** in 68% overall yield for two steps, after a simple aqueous work-up and flash column chromatography (Table 1, entry



Scheme 2. Cyclization of triazene **6** to triazole **7**.



Scheme 3. (a) 10.0 equiv. of Cs_2CO_3, 10.0 equiv. of 4-hydroxybenzaldehyde, 85°C, DMF, 12 h; (b) 10.0 equiv. of phenyl hydrazine, 10.0 equiv. of BF_3. Et_2O, DMF, room temperature, 12 h; (c) 7.0 equiv. of NCS, 14.0 equiv. of DMS, CH_2Cl_2 0 to −78°C to room temperature; (d) 20.0 equiv. of **5**, CH_3CN, room temperature; 12 h; (e) 10.0 equiv. of DMP, CH_2Cl_2, room temperature, 12 h: (f) 1.0 equiv. of TPAP/12.0 equiv. of NMO, CH_3CN, room temperature, 12 h; (g) 95:5 TFA/H_2O, 2 h, room temperature.

1). Comparison of the LC/MS data of the reaction mixture before and after the addition of NaClO clearly indicated that NaClO was essential to promote the cyclization. Similar to NaClO, reaction of the triazene **6a** with commercially available solid $Ca(ClO)_2$ (calcium hypochlorite, Lancaster)[10] in CH_3CN for 24 h also smoothly promoted the cyclization and furnished the triazole **7a** in 65% overall yield for two steps, after removal of the solvent and purification (Table 1, entry 1). The above yields (68 and 65%) are comparable with the yield of **7a** (69%) obtained using Ag_2CO_3 method[5] (shown in Table 1, entry 1 for comparison), which clearly indicates that the NaClO and $Ca(ClO)_2$ mediated triazole syntheses are as efficient as the Ag_2CO_3 method.[5] In addition to the mild reaction condition and simple work-up procedure, the reagents, NaClO and $Ca(ClO)_2$, are commercially available, inexpensive and environmentally friendly, which make this approach superior to our previously reported Ag_2CO_3 method.[5]

Having isolated the triazole **7a** in good yields using the hypochlorite oxidizing agents, we then extended our study to other commercially available and commonly used oxidizing reagents such as DMP[11] and TPAP/NMO.[12] Although these two reagents have been extensively used in organic synthesis as oxidizing agents to prepare aldehydes and ketones from the corresponding primary and secondary alcohols, respectively, the synthetic usefulness of these reagents to perform other chemical transformations has not been fully exploited. While our study was in progress, Nicolaou et al. reported a DMP and 2-iodoxybenzoic acid (IBX)[15] induced cyclization of unsaturated anilides to prepare various nitrogen heterocycles.[16,17] The oxidizing property, solubility in organic solvents and ease of handling encouraged us to choose the above reagents for our cyclization study. Treatment of the triazene **6a** with 1.5 equiv. of DMP in CH_2Cl_2 or 0.2 equiv. of TPAP and 1.5 equiv. of NMO in CH_3CN for 3 h smoothly promoted the cyclization and provided the triazole **7a** in 81 and 79% yields, respectively, after purification. The reactions were very clean and did not require any aqueous work-up. Removal of the solvent followed by purification of the crude reaction mixture provided the triazole **7a**. It is important to note that in the absence of TPAP, NMO did not promote the cyclization of triazene **6a**, which clearly indicated the important role of TPAP in the cyclization reaction. To our knowledge, these are the first examples utilizing oxidizing reagents DMP and TPAP/NMO to convert 1,2,4-triazene to 1,2,4-triazole. The yields of triazole **7a** obtained using DMP and TPAP/NMO methods (81 and 79%, respectively) are superior to the yield (69%) obtained using the Ag_2CO_3 method (Table 1, entry 1). Since IBX has been shown to have oxidizing property similar to DMP, IBX would also be expected to promote the cyclization of triazene **6** to triazole **7**. Buzykin et al. proposed a mechanism to account for the formation of triazoles through cyclization of triazenes in the presence of an oxidizing reagent (Scheme 2).[4] The key role

of an oxidizing reagent in this reaction is to oxidize the triazene **6** into an azoimine intermediate **A**, which then undergoes tautomerization, cyclization and oxidation in a tandem sequence to provide the triazole **7**. However, no further mechanistic study was carried out to confirm the proposed mechanism in Scheme 2.

To further probe the synthetic scope of our oxidizing agent promoted triazole synthesis, the reaction was then extended to triazenes with different functional groups **6b–d**, prepared from hydrazonyl chloride **4** and amines **5b–d** (Table 1, entries 2–4). Reaction of triazenes **6b–d** with the above oxidizing agents proceeded smoothly and yielded the desired triazoles **7b–d** in moderate to high yields (Table 1, entries 2–4). Under the reaction conditions, the presence of vinyl and pyridyl groups did not yield the corresponding epoxide and *N*-oxide products, respectively, as evident from the LC/MS data of the reaction mixtures (Table 1, entries 2 and 3). The vinyl and ester functionalities present in triazoles **7b** and **d**, respectively, could be used as handles to introduce additional structural diversity.

Next we turned our attention to examine the adaptability of this approach to solid-phase synthesis, which would allow preparation of combinatorial libraries of 1,2,4-triazoles.[6,7] Since DMP and TPAP/NMO are soluble in organic solvents, they were chosen as the reagents of choice for our solid-phase triazole synthesis. Acid cleavable ArgoGel–Wang–Cl (loading 0.39 mmol/g) resin **8** was selected to carry out the solid-phase triazole synthesis (Scheme 3). Treatment of **8** with 10.0 equiv. of 4-hydroxybenzaldehyde in the presence of 10.0 equiv. of Cs_2CO_3 in DMF at 85°C for 12 h provided the resin-bound aldehyde **9**, which was then condensed with phenylhydrazine (**2**) in the presence of BF_3. Et_2O (10.0 equiv.) to provide the hydrazone **10**. Initial attachment of 4-hydroxybenzaldehyde moiety on solid support and conversion of the aldehyde **9** to hydrazone **10** were readily monitored by the appearance and disappearance of the aldehyde signal in the solid phase magic angle spinning (SPMAS) NMR spectrum.[18] Reaction of the resin-bound hydrazone **10** with 7.0 equiv. of NCS/DMS complex provided the resin-bound hydrazonyl chloride **11**, which was then treated with amines **5a**, **b**, **e**, **f** to give the corresponding triazenes **12a–d**. Treatment of the triazenes **12a–d** with DMP or TPAP/NMO smoothly promoted the cyclization and furnished the corresponding resin-bound triazoles **13a–d**, which upon treatment with 95% TFA followed by chromatographic purification provided the triazoles **14a–d** in 16–47% overall yields for six steps (Scheme 3). In the case of triazenes **12b** and **c**, the triazoles **14b** and **c** were isolated in low yields as a result of the formation a 1,3-disubstituted triazole[5] as the side product. No further optimization study was carried out to improve the yields of triazoles **14b** and **c**. Commercial availability of diverse primary amines, hydrazines and hydroxybenzaldehydes makes this approach very attractive to prepare large numbers of 1,2,4-triazoles in a short period of time.

3. Conclusion

We have described an efficient approach to 1,3,5-trisubstituted 1,2,4-triazoles through cyclization of 1,2,4-triazenes using readily available and commonly used oxidizing agents such as NaClO, $Ca(ClO)_2$, DMP and TPAP/NMO. The reactions were carried out under mild reaction conditions and the products were isolated in moderate to good yields. The approach was successfully extended to prepare triazoles on solid-support, which would allow preparation of combinatorial libraries of 1,2,4-triazoles. Construction of combinatorial libraries of triazoles on solid support and biological activities will be reported in due course.

4. Experimental

4.1. 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. DMP and $Ca(ClO)_2$ were purchased from Lancaster. TPAP and NaClO were obtained from Aldrich. ArgoGel–Wang–Cl was obtained from Argonaut Technologies.

4.2. General procedure for the preparation of triazenes 6a–d: representative procedure for compound 6a

To a solution of hydrazonyl chloride (250 mg, 1.09 mmol, 1 equiv.) in CH_3CN (10 mL) were added benzylamine (**5a**) (0.14 g, 1.31 mmol, 1.2 equiv.) and TEA (0.13 g, 1.31 mmol, 1.2 equiv.) and the reaction mixture was stirred at room temperature for 15 h. Removal of the solvent and excess TEA provided the crude triazene **6a**, which was then subjected to the cyclization condition.

4.3. Typical procedure for the preparation of triazoles 7a–d using NaClO: representative procedure for compound 7a

To a solution of the crude triazene **6a** (1.09 mmol) in CH_3CN (10 mL) was added NaClO solution (5 mL) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (25 mL) and washed with H_2O (1×20 mL). The organic layer was drained, dried and evaporated, and the residue was purified by flash column chromatography (hexane/20% EtOAc) to provide triazole **7a** (0.220 g, 68% yield).

4.4. Typical procedure for the preparation of triazoles 7a–d using $Ca(ClO)_2$: representative procedure for compound 7a

To a solution of the crude triazene **6a** (1.09 mmol, 1.0 equiv.) in CH_3CN (10 mL) was added $Ca(ClO)_2$ (0.31 g, 2.18 mmol, 2.0 equiv.) and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/20% EtOAc) to provide triazole **7a** (0.210 g, 65% yield).

4.5. Typical procedure for the preparation of triazoles 7a–d using Dess–Martin periodinane: representative procedure for compound 7a

To a solution of the crude triazene **6a** (1.09 mmol) in CH_2Cl_2 (10 mL) was added DMP (0.69 g, 1.64 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/20% EtOAc) to provide triazole **7a** (0.262 g, 81% yield).

4.6. Typical procedure for the preparation of triazoles 7a–d using TPAP/NMO: representative procedure for compound 7a

To a solution of the crude triazene **6a** (1.09 mmol) in CH_3CN (10 mL) were added TPAP (77.0 mg, 0.22 mmol, 0.2 equiv.) and NMO (0.19 g, 1.64 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was purified by flash column chromatography (hexane/20% EtOAc) to provide triazole **7a** (0.256 g, 79% yield).

4.7. Preparation of aldehyde 9

To a suspension of ArgoGel–Wang–Cl resin **8** (loading 0.39 mmol/g, 12.0 g, 4.68 mmol, 1 equiv.) in DMF (100 mL) were added 4-hydroxybenzaldehyde (5.72 g, 46.80 mmol, 10 equiv.) and cesium carbonate (15.25 g, 46.80 mmol, 10 equiv.) and the reaction mixture was heated at 85°C for 12 h. Excess reagents were drained, and the resin was washed with 1:1 H_2O/DMF (3×80 mL) and DMF (3×80 mL) to provide the resin-bound aldehyde **9**.

4.8. Preparation of hydrazone 10

To a suspension of **9** (2.34 mmol, 1 equiv.) in DMF (60 mL) were added phenylhydrazine (2.53 g, 23.40 mmol, 10 equiv.) and $BF_3{\cdot}Et_2O$ (3.32 g, 23.40 mmol, 10.0 equiv.), and the reaction mixture was agitated at room temperature for 12 h. Excess reagents were drained, and the resin was washed with DMF (3×50 mL) and CH_2Cl_2 (2×50 mL) to provide the resin-bound hydrazone **10**.

4.9. Preparation of hydrazonyl chloride 11

To a solution of *N*-chlorosuccinimide (2.18 g, 16.38 mmol, 7 equiv.) in CH_2Cl_2 (80 mL) at 0°C was added dimethyl sulfide (2.06 g, 32.76 mmol, 14 equiv.), and the mixture was stirred at 0°C for 10 min. Then the reaction was cooled to −78°C and the resin-bound hydrazone **10** (2.34 mmol, 1 equiv.) was added and the mixture was gently stirred at −78°C for 1 h, and then slowly warmed to room temperature and stirred for additional 3 h. Excess reagents were drained and the resin was washed with CH_2Cl_2 (3×50 mL) to give the resin-bound hydrazonyl chloride **11**.

4.10. General procedure for the preparation of triazene 12

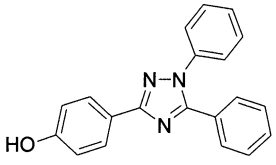
To a suspension of the resin-bound hydrazonyl chloride **11** (1.17 mmol, 1 equiv.) in CH_3CN (17 mL) was added an amine (**5a**, **b**, **e**, **f**, 23.40 mmol, 20.0 equiv.) and the reaction mixture was agitated at room temperature for 12 h. Excess amine was drained and the resin was washed with DMF (3×30 mL) and CH_2Cl_2 (3×30 mL) to give the corresponding triazene (**12a**–**d**).

4.11. General procedure for the preparation of triazoles 14a–d using Dess–Martin periodinane

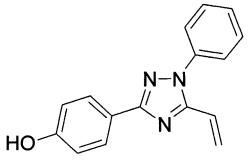
To a suspension of a triazene (**12a**–**d**) (0.59 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) was added DMP (2.50 g, 5.9 mmol, 10 equiv.) and the mixture was agitated at room temperature for 12 h. Excess reagents were drained and the resin was washed with DMF (3×20 mL), MeOH (3×20 mL), and CH_2Cl_2 (3×20 mL). Treatment of the resin with 95% TFA (20 mL) at room temperature for 2 h followed by removal of TFA and purification (hexane/EtOAc) provided the corresponding triazole (**14a**–**d**).

4.12. General procedure for the preparation of triazoles 14a–d using NMO/TPAP

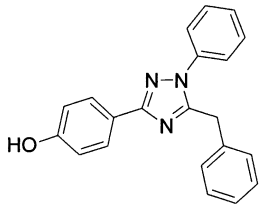
To a suspension of a triazene (**12a**–**d**) (0.59 mmol, 1 equiv.) in CH_3CN (30 mL) were added NMO (0.83 g, 7.08 mmol, 12 equiv.) and TPAP (0.21 g, 0.59 mmol, 1 equiv.), and the reaction mixture was agitated at room temperature for 12 h. Excess reagents were drained and the resin was washed with DMF (3×20 mL), MeOH (3×20 mL) and CH_2Cl_2 (3×20 mL). Treatment of the resin with 95% TFA (20 mL) at room temperature for 2 h followed by removal of TFA and purification (hexane/EtOAc) provided the corresponding triazole (**14a**–**d**).



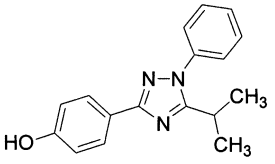
4.12.1. Compound 14a. ^{1}H NMR (DMSO-d_6) δ 6.88 (d, J=8.8 Hz, 2H), 7.39–7.52 (m, 10H), 7.93 (d, J=8.8 Hz, 2H), 9.82 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 115.5, 121.4, 125.7, 127.6, 127.8, 128.6, 128.7, 129.1, 129.5, 130.0, 138.0, 154.2, 158.7, 161.0; HRMS *m/z* calcd for $C_{20}H_{15}N_3O$ 313.1215, found 313.1222.



4.12.2. Compound 14b. ^{1}H NMR (DMSO-d_6) δ 5.72 (d, J=11.2 Hz, 1H), 6.34 (d, J=17.2 Hz, 1H), 6.63 (dd, J=17.2, 11.2 Hz, 1H), 6.86 (d, J=8.4 Hz, 2H), 7.55–7.64 (m, 5H), 7.90 (d, J=8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 115.5, 121.4, 121.8, 123.6, 125.3, 127.6, 129.1, 129.6, 136.7, 152.3, 158.7, 160.9; HRMS *m/z* calcd for $C_{16}H_{13}N_3O$ 263.1059, found 263.1065.



4.12.3. Compound 14c. ^{1}H NMR (DMSO-d_6) δ 4.22 (s, 2H), 6.84 (d, J=8.4 Hz, 2H), 7.12 (d, J=7.2 Hz, 2H), 7.19 (m, 1H), 7.26 (m, 2H), 7.49–7.57 (m, 5H), 7.85 (d, J=8.8 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 31.9, 115.5, 121.6, 125.0, 126.6, 127.5, 128.4, 128.5, 128.9, 129.5, 136.2, 137.1, 154.8, 158.5, 160.6; HRMS *m/z* calcd for $C_{21}H_{17}N_3O$ 327.1372, found 327.1365.



4.12.4. Compound 14d. ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J=6.4 Hz, 6H), 3.18 (m, 1H), 6.78 (dd, J=8.8, 2.0 Hz, 2H), 7.46 (m, 2H), 7.52–7.58 (m, 3H), 7.88 (dd, J=8.8, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.1, 116.1, 120.3, 126.0, 128.6, 129.9, 130.0, 136.8, 158.9, 160.3, 161.5; HRMS *m/z* calcd for $C_{17}H_{17}N_3O$ 279.1372, found 279.1366.

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References

1. Source: MDL Drug Data Registry, by MDL information Systems, Inc.; San Leandro, CA, USA.
2. (a) Kaku, Y.; Tsuruoka, A.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 1125. (b) Tanoury, G. J.; Senanayake, C. H.; Hett, R.; Kuhn, A. M.; Kessler, D. W.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 6845. (c) Koltin, Y.; Hitchcock, C. A. *Curr. Opin. Chem. Biol.* **1997**, *1*, 176. (d) Zirngibl, L. *Antifungal Azoles: A Comprehensive Survey of their Structures and Properties*; Wiley-VCH: New York, 1998.
3. Sui, Z.; Guan, J.; Hlasta, D. J.; Macielag, M. J.; Foleno, B. D.; Goldschmidt, R. M.; Loeloff, M. J.; Webb, G. C.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1929.
4. Buzykin, B. I.; Bredikhina, Z. A. *Synthesis* **1993**, 59.
5. Paulvannan, K.; Chen, T.; Hale, R. *Tetrahedron* **2000**, *56*, 8071.
6. For recent reviews on SPOS, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385. (c) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (d) Corbett, J. W. *Org. Prep. Proced. Int.* **1998**, *30*, 491. (e) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*; Gordon, E. M., Kerwin, Jr., J. F., Eds.; Wiley-Liss: New York, 1998.
7. Triazoles on solid support: (a) Katritzky, A. R.; Qi, M.; Feng, D.; Zhang, G.; Griffith, M. C.; Watson, K. *Org. Lett.* **1999**, *1*, 1189. (b) Wilson, M. W.; Hernandez, A. S.; Calvet, A. P.; Hodges, J. C. *Mol. Diversity* **1998**, *3*, 95.
8. (a) Stevens, R. V.; Chapman, K. T. *Tetrahedron Lett.* **1982**, *23*, 4647. (b) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030.
9. For a review on oxidations with hypochlorites, see: Skarzewski, J.; Siedlecka, R. *Org. Prep. Proced. Int.* **1992**, *24*, 623.
10. (a) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 35. (b) Nwaukwa, S. O.; Keehn, P. M. *Tetrahedron Lett.* **1982**, *23*, 3131. (c) McDonald, C. E.; Nice, L. E.; Shaw, A. W.; Nestor, N. B. *Tetrahedron Lett.* **1993**, *34*, 2741.
11. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Ireland, R. E.; Liu, L. J. *J. Org. Chem.* **1993**, *58*, 2899. (d) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.
12. (a) Griffith, W. P.; Ley, S.; Whitecombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Boons, G.; Brown, D. S.; Clase, J. A.; Lennon, I. C.; Ley, S. V. *Tetrahedron Lett.* **1994**, *35*, 319. (c) Goti, A.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6567. (d) Goti, A.; De Sarlo, F.; Romani, M. *Tetrahedron Lett.* **1994**, *35*, 6571. (e) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
13. Patel, H. V.; Vyas, K. A.; Pandey, S. P.; Fernandes, P. S. *Tetrahedron* **1996**, *52*, 661.
14. (a) Balogh, V.; Fetizon, M.; Golfier, M. *J. Org. Chem.* **1971**, *36*, 1339. (b) Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523.
15. (a) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. (b) Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. (c) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (d) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727.
16. Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 622.
17. (a) Nicolaou, K. C.; Zhong, Y.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 625. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2525. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183.
18. (a) Yan, B. *Analytical Methods in Combinatorial Chemistry*; Technomic: Pennsylvania, 2000. (b) Claridge, T. D. W. In *High-Resolution NMR Techniques in Organic Chemistry*; Baldwin, J. E., Williams, F. R. S., Williams, R. M., Eds.; *Tetrahedron Organic Chemistry Series*; Pergamon: New York, 1999; Vol. 19. (c) Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J.; Keifer, P. A. *J. Org. Chem.* **1994**, *59*, 7955.