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Regiospecific solid-phase synthesis of substituted 1,2,3-triazoles

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Abstract—A traceless and regiospecific solid-phase synthesis of substituted 1,2,3-triazoles is developed using polystyrene-sulfonyl hydrazide resin. The chemistry is applicable to combinatorial library synthesis.

1,2,3-Triazoles are useful targets in chemical synthesis as they have been associated with a wide variety of interesting properties. Members of this class of compound are known to possess β-lactamase inhibitory,[1] antiHIV,[2] antimicrobial,[3] antiviral and antiepileptic[4] activities. They have also found fruitful applications as light stabilizers, fluorescent whiteners, precursors of insecticides for industry, optical brightening and corrosion retarding agents.[5] Consequently, methodologies for the preparation of 1,2,3-triazoles have attracted much attention from both industry and academia, and numerous solution-phase syntheses of these compounds have been reported.[6] In recent years, synthetic methods for the preparation of 1,2,3-triazoles on solid-phase have been examined.[6–12] Most of these solid-phase syntheses involve linkers, which would leave a tether on the final product, which is sometimes undesirable. Recently two reports on the traceless synthesis of 1,2,3-triazoles were published.[11,12] Both papers reported the preparation of 1,2,3-triazoles using 1,3-dipolar cycloaddition between an alkyne and an azide. However, the regioselectivities of these cycloaddition reactions varied dramatically, depending on the nature of the alkyne used. Thus, new methods providing an improvement in the regioselectivity of the solid-phase synthesis of 1,2,3-triazoles would be of interest.

The synthesis of 1,2,3-triazoles could be achieved through the intramolecular cyclization of a diazo intermediate[13] which, in turn, could be generated from the Bamford–Stevens reaction[14] between a tosyl hydrazone and a base. Nevertheless, to our knowledge, this methodology has not been employed for solid-phase 1,2,3-triazole synthesis. We herein describe a traceless solid-phase approach to substituted 1,2,3-triazoles via α-substituted carbonyl sulfonylhydrazones. Depending on the α-substituent used, a variety of substituted 1,2,3-triazoles can be conveniently prepared (Table 1).

Polystyrene–sulfonyl hydrazide (PS–Ts–$NHNH_2$) **1** is commonly used as a carbonyl scavenging resin. Its function as a linker for solid-phase synthesis is less well-explored with only one paper documenting its use as a linker in solid-phase synthesis.[15] In our preliminary solid-phase study, two reaction systems were examined for the formation of the polymer bound α-dichloro carbonyl sulfonylhydrazone **2** from **1** (Scheme 1). Treatment of **1** in THF with 1,1-dichloroacetone in the presence of 10% acetic acid for 4 h at 50 °C gave **2**, which was subsequently reacted with cyclooctylamine to give 1-cyclooctyl-4-methyl-1*H*-[1,2,3]-triazole **3a** in 44% yield. However replacement of the 10% acetic acid with 5% $TiCl_4/CH_2Cl_2$ in methanol gave an improved yield of **3a** (57%). The latter procedure[16] was thus used for the library synthesis.

As an application of this reaction, we prepared 1,5-disubstituted-1,2,3-triazoles in the same manner. Reaction of **1** with 1,1,1-trichloroacetaldehyde gave **4**, which was then treated with excess amine to give **5**, however in lower yields.

To demonstrate the versatility of this methodology, we proceeded to prepare fused triazoles. Reaction of **1** with heterocyclic carbonyl compounds like 2-acetylpyridine, pyridine-2-carboxaldehyde, 1-thiazol-2-yl-ethanone or

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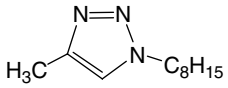
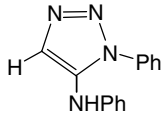
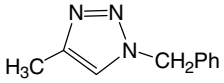
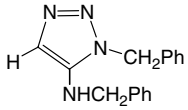
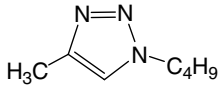
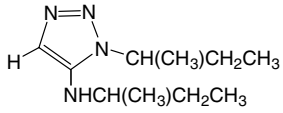
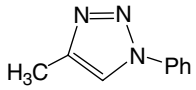
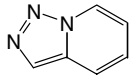
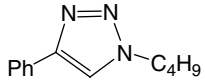
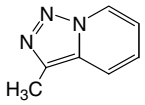
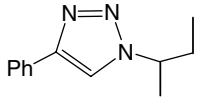
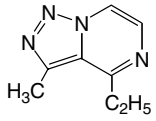
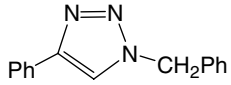
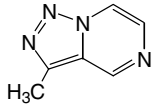
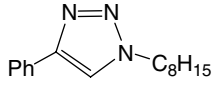
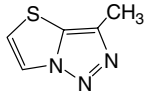
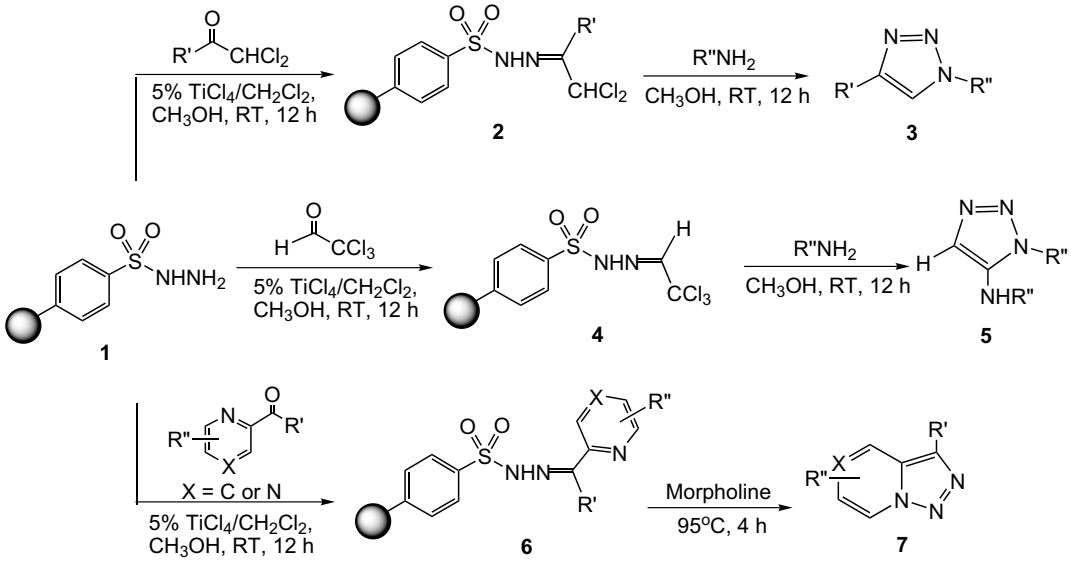
Table 1. Solid-phase synthesis of 1,2,3-triazoles **3**, **5** and **7**

Entry	Compound	% Yield[a]	Entry	Compound	% Yield[a]
3a		57	**5a**[b]		17
3b		53	**5b**		14
3c		51	**5c**		11
3d		47	**7a**		41
3e		28	**7b**		62
3f		32	**7c**[b]		33
3g[b]		31	**7d**		50
3h		32	**7e**		60

[a] Purified yield calculated based on original loading of the resin. Purities of >95% as evaluated by NMR.
[b] Crystallographic data (excluding structure factors) for **3g**, **5a** and **7c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 231980, CCDC 231982 and CCDC 231981, respectively.



Scheme 1.

acetylpyrazine derivatives in 5% $TiCl_4/CH_3OH$ gave hydrazones **6**. Subsequent treatment of **6** with morpholine at 95 °C gave fused triazoles **7** in 33–62% overall yields.

In summary, this paper demonstrates a general protocol for the regiospecific and traceless solid-phase synthesis of 1,2,3-triazole derivatives using α-polychloro carbonyl sulfonylhydrazones and amines. Further developments are in progress.

References and notes

1. Im, C.; Maiti, S. N.; Micetich, R. G.; Daneshtalab, M.; Atchison, K.; Phillips, O. A. *J. Antibiot.* **1994**, *47*, 1030–1040.
2. Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camaraza, M. *J. Antivir. Chem. Chemother.* **1998**, *9*, 481–489.
3. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.
4. Palhagen, S.; Canger, R.; Henriksen, O.; van Parys, J. A.; Riviere, M.-E.; Karolchyk, M. A. *Epilepsy Res.* **2001**, *43*, 115–124.
5. Fan, W. Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 4, pp 1–126.
6. Gouault, N.; Cupif, J. F.; Sauleau, A.; David, M. *Tetrahedron Lett.* **2000**, *41*, 7293–7297.
7. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
8. Moore, M.; Norris, P. *Tetrahedron Lett.* **1998**, *39*, 7027–7030.
9. Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 10823–10826.
10. Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Hunn, C. L.; Natchus, M. G.; Parket, M. S.; Portluck, D. E.; Tullis, J. S.; Wood, J. *Tetrahedron Lett.* **2002**, *434*, 4059–4061.
11. Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-Kauhaluoma, J. *J. Comb. Chem.* **2003**, *5*, 826–833.
12. Garanti, L.; Molten, G. *Tetrahedron Lett.* **2003**, *44*, 1133–1135.
13. Sakai, K.; Hida, N.; Kondo, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 179–183.
14. Shapiro, R. H. *Org. React.* **1976**, *23*, 405–407.
15. Hu, Y.; Baudart, S.; Proco, J. A., Jr. *J. Org. Chem.* **1999**, *64*, 1049–1051.
16. Typical experimental procedure: **1** was swollen in a mixture containing 9.5 mL CH_3OH and 0.5 mL of a 1 M solution of $TiCl_4$ in CH_2Cl_2 for 1 h. The carbonyl compound (5 equiv) was added and the reaction mixture was then shaken at room temperature for 12 h. The resin was then filtered and washed consecutively with CH_3OH (20 mL × 2), H_2O (20 mL × 2), acetone (20 mL × 2), and EtOAc (20 mL × 2), and dried overnight in a vacuum oven at 40 °C. Dry resin **2** was swollen in 10 mL CH_3OH for 1 h. The amine (10 equiv) was then added and the reaction mixture was shaken at room temperature for 24 h (for **7**, dry resin **6** (1 g) was swollen in morpholine (10 mL) and then heated at 95 °C for 6 h), after which, the resin was filtered and washed with CH_3OH (20 mL × 2). The combined filtrate was evaporated and purified by column chromatography to give **3**, **5** or **7**. The compounds were analysed by NMR (in $CDCl_3$) and HRMS. Compound **3a**. ^{1}H NMR: δ 1.63 (br s, $8H_{cyclooctyl}$), 1.75–1.85 (br m, $2H_{cyclooctyl}$), 2.04–2.08 (br m, $4H_{cyclooctyl}$), 2.33 (s, 3H, CH_3), 4.63–4.74 (m, $1H_{cyclooctyl}$), 7.28 (s, $1H_{pyrazole}$). ^{13}C NMR: δ 10.80, 24.02, 25.59, 26.66, 33.15, 61.25, 118.89, 142.86. HRMS (EI): Calcd for $C_{11}H_{19}N_3$ 193.1579, found 193.1578. Compound **3b**: ^{1}H NMR: δ 2.37 (s, 3H, CH_3), 5.52 (s, 2H, CH_2Ph), 7.21 (s, $1H_{pyrazole}$), 7.24–7.27 (m, 2H, ArH), 7.34–7.37 (m, 3H, ArH). ^{13}C NMR: δ 10.76, 53.96, 121.1, 127.94, 128.01, 128.60, 128.73, 129.01, 129.09, 143.68. HRMS (EI): Calcd for $C_{10}H_{11}N_3$ 173.0953, found 173.0953. Compound **3c**: ^{1}H NMR: δ 0.93–0.97 (t, $J = 7.31$ Hz, $3H_{butyl}$, CH_3), 1.29–1.41 (m, $2H_{butyl}$, CH_2), 1.82–1.92 (m, $2H_{butyl}$, CH_2), 2.37 (s, 3H, CH_3), 4.30–4.34 (t, $J = 7.14$ Hz, $2H_{butyl}$), 7.28 (s, $1H_{pyrazole}$). ^{13}C NMR: δ 10.57, 13.24, 19.49, 32.12, 49.65, 120.85, 143.00. HRMS (EI): Calcd for $C_7H_{13}N_3$ 139.1109, found 139.1107. Compound **3d**: ^{1}H NMR: δ 2.42 (s, 3H, CH_3), 7.36–7.42 (m, 1H, ArH), 7.46–7.51 (m, 2H, ArH), 7.67–7.72 (m, 3H, $2ArH + 1H_{pyrazole}$). ^{13}C NMR: δ 10.78, 119.33, 120.32, 128.40, 129.61, 137.14, 144.01. HRMS (EI): Calcd for $C_9H_9N_3$ 159.0796, found 159.0794. Compound **3e**: ^{1}H NMR: δ 0.94–0.99 (t, $J = 7.49$ Hz, $3H_{butyl}$, CH_3), 1.33–1.45 (m, $2H_{butyl}$, CH_2), 1.88–1.95 (m, $2H_{butyl}$, CH_2), 4.37–4.42 (t, $J = 7.14$ Hz, $2H_{butyl}$, NCH_2), 7.30–7.35 (m, 1H, ArH), 7.39–7.45 (m, 2H, ArH), 7.75 (s, $1H_{pyrazole}$), 7.82–7.84 (d, $J = 8.36$ Hz, 2H, ArH). ^{13}C NMR: δ 12.99, 19.24, 31.80, 49.78, 119.08, 125.26, 127.71, 128.37, 128.65, 129.09, 129.98, 147.10. HRMS (EI): Calcd for $C_{12}H_{15}N_3$ 201.1266, found 201.1264. Compound **3f**: ^{1}H NMR: δ 0.86–0.91 (t, $J = 7.49$ Hz, $3H_{butyl}$, CH_3), 1.59–1.61 (d, $J = 6.97$ Hz, $3H_{butyl}$, CH_3), 1.85–2.03 (m, $2H_{butyl}$, CH_2), 4.57–4.69 (m, $1H_{butyl}$, NCH), 7.29–7.34 (m, 1H, ArH), 7.39–7.44 (t, 2H, ArH), 7.75 (s, $1H_{pyrazole}$), 7.83–7.86 (d, $J = 8.32$ Hz, 2H, ArH) ^{13}C NMR: δ 10.42, 20.95, 30.29, 117.42, 125.64, 128.04, 128.78, 130.67, 147.40. HRMS (EI): Calcd for $C_{12}H_{15}N_3$ 201.1266, found 201.1262. Compound **3g**: ^{1}H NMR: δ 5.58 (s, 2H, NCH_2), 7.30–7.42 (br m, 8H, ArH), 7.67 (s, $1H_{pyrazole}$), 7.79–7.82 (d, $J = 8.71$ Hz, 2H, ArH). ^{13}C NMR: δ 53.66, 119.10, 124.74, 125.47, 126.08, 129.97, 134.17, 147.64. HRMS (EI): Calcd for $C_{15}H_{13}N_3$ 235.1109, found 235.1104. Compound **3h**: ^{1}H NMR: δ 1.66 (br s, $8H_{cyclooctyl}$), 1.82–1.89 (m, $2H_{cyclooctyl}$), 2.10–2.18 (m, $4H_{cyclooctyl}$), 4.71–4.83 (m, $1H_{cyclooctyl}$), 7.31–7.33 (m, 1H, ArH), 7.39–7.43 (m, 2H, ArH), 7.74 (s, $1H_{pyrazole}$), 7.81–7.83 (d, $J = 7.31$ Hz, 2H, ArH). ^{13}C NMR: δ 24.08, 26.64, 27.75, 33.23, 61.64, 117.36, 126.62, 127.94, 128.76. HRMS (EI): Calcd for $C_{16}H_{21}N_3$ 255.1735, found 255.1734. Compound **5a**: ^{1}H NMR: δ 5.82 (s, 1H, NH), 6.94–7.00 (m, 3H, ArH), 7.26–7.31 (t, $J = 8.01$ Hz, 2H, ArH), 7.53–7.56 (m, 6H, $5ArH + 1H_{pyrazole}$). ^{13}C NMR: δ 113.33, 116.33, 121.66, 121.98, 124.52, 128.22, 129.47, 129.60, 129.83, 135.06, 138.25, 141.61. HRMS (EI): Calcd for $C_{14}H_{12}N_4$ 236.1062, found 236.1062. Compound **5b**: ^{1}H NMR: δ 4.20 (s, 2H, CH_2Ph), 5.42 (s, 2H, CH_2Ph), 6.98 (s, 1H, NH), 7.10–7.13 (br m, 2H, ArH), 7.18–7.21 (br m, 2H, ArH), 7.23–7.30 (br m, 4H, $3ArH + 1H_{pyrazole}$), 7.34–7.37 (m, 3H, ArH). ^{13}C NMR: δ 49.93, 50.56, 127.23, 127.30, 127.80, 128.58, 128.74, 129.24. HRMS (EI): Calcd for $C_{16}H_{16}N_4$ 264.1375, found 264.1376. Compound **5c**: ^{1}H NMR: δ 0.77–0.82 (2t, $J = 7.32$ Hz, 6H, CH_3 of 2 diastereoisomers), 0.87–0.92 (2t, $J = 7.32$ Hz, 6H, CH_3 of 2 diastereoisomers), 1.13–1.16 (2d, $J = 6.27$ Hz, 6H, CH_3 of 2 diastereoisomers), 1.46–1.49 (2d, $J = 6.97$ Hz, 6H, CH_3 of 2 diastereoisomers), 1.75–1.85 (2m, 4H, CH_2 of 2 diastereoisomers),

1.92–2.02 (2m, 4H, CH_2 of 2 diastereoisomers), 3.11–3.27 (2m, 2H, NCH of 2 diastereoisomers), 4.05–4.13 (2m, 2H, NCH of 2 diastereoisomers), 6.90–6.91 (2s, 2H, ArH). ^{13}C NMR: δ 10.15, 10.67, 20.03, 20.25, 29.17, 29.54, 29.58, 53.18, 54.55, 117.39. HRMS (EI): Calcd for $C_{10}H_{20}N_4$ 196.1688, found 196.1686. Compound **7a**: ^1H NMR: δ 6.89–6.93 (t, $J = 6.79$ Hz, 1H, ArH), 7.15–7.21 (t, $J = 7.66$ Hz, 1H, ArH), 7.65–7.67 (d, $J = 8.71$ Hz, $1H_{pyrazole}$), 7.98 (s, 1H, ArH), 8.65–8.68 (d, $J = 7.32$ Hz, 1H, ArH). ^{13}C NMR: δ 115.06, 117.68, 124.87, 125.01, 125.31. HRMS (EI): Calcd for $C_6H_5N_3$ 119.0483, found 119.0480. Compound **7b**: ^1H NMR: 2.62 (s, 3H, CH_3), 6.90–6.94 (t, $J = 6.79$ Hz, 1H, ArH), 7.14–7.19 (t, $J = 7.83$ Hz, 1H, ArH), 7.60–7.63 (d, $J = 8.71$ Hz, 1H, ArH), 8.63–8.66 (d, $J = 6.97$ Hz, 1H, ArH). ^{13}C NMR: δ 10.25, 14.99, 17.46, 123.65, 125.01, 131.56, 134.24. HRMS (EI): Calcd for $C_7H_7N_3$ 133.0640, found 133.0637. Compound **7c**: ^1H NMR: δ 1.39–1.44 (t, $J = 7.49$ Hz, $3H_{ethyl}$, CH_3), 2.82 (s, 3H, CH_3), 3.17–3.24 (q, $J = 7.43$ Hz, $2H_{ethyl}$, CH_2), 7.82–7.83 (d, $J = 4.87$ Hz, 1H, ArH), 8.39–8.41 (d, $J = 4.88$ Hz, 1H, ArH). ^{13}C NMR: δ 11.88, 12.85, 29.02, 116.45, 127.28, 131.01, 137.32, 145.08. HRMS (EI): Calcd for $C_8H_{10}N_4$ 162.0905, found 162.0909. Compound **7d**: ^1H NMR: δ 2.73 (s, 3H, CH_3), 7.94–7.96 (d, $J = 4.88$ Hz, 1H, ArH), 8.53–8.58 (dd, $J = 6.62$, 1.75 Hz, 1H, ArH), 9.18 (s, 1H, ArH). ^{13}C NMR: δ 10.39, 118.06, 127.36, 131.22, 137.39, 145.05. HRMS (EI): Calcd for $C_6H_6N_4$ 134.0592, found 134.0594. Compound **7e**: ^1H NMR: δ 2.49 (s, 3H, CH_3), 7.15–7.17 (d, $J = 4.18$ Hz, 1H, CH), 7.95–7.97 (d, $J = 4.18$ Hz, 1H, CH). ^{13}C NMR: δ 11.00, 119.27, 119.98 132.63, 134.14. HRMS (EI): Calcd for $C_5H_5N_3S$ 139.0204, found 139.0206.