Solid phase synthesis of 4,5-disubstituted 1,2,4-triazol-3-one derivatives from resin-bound acylhydrazines

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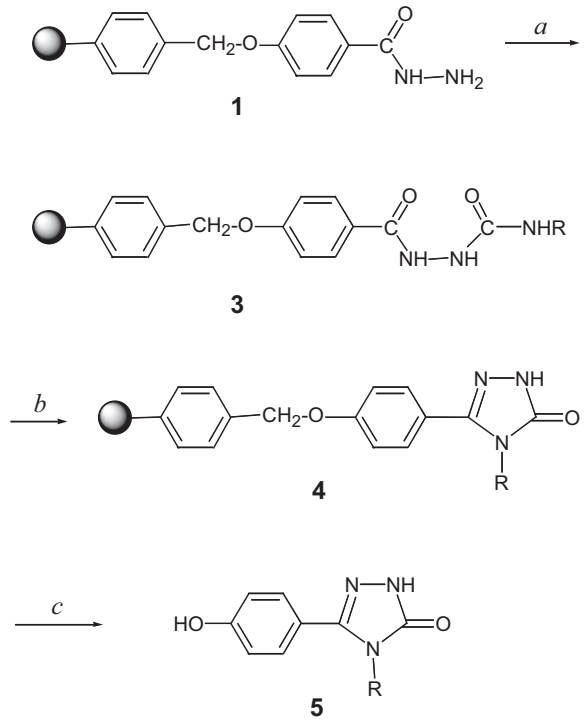
A new strategy for solid-phase synthesis of 4,5-disubstituted 2,4-dihydro-3*H*-1,2,4-triazol-3-ones has been developed. The 4-substituted 5-(4-hydroxyphenyl)-1,2,4-triazol-3-one derivatives were synthesised from resin-bound acylhydrazines in several steps, in good overall yields and purity.

Keywords: solid phase synthesis, 1, 2, 4-triazol-3-ones, resin-bound acylhydrazine

With the availability of automated techniques, the solid phase synthesis of small organic molecules is becoming an important method for the rapid and easy preparation of libraries of organic compounds in order to accelerate drug discovery processes.[1-3] This approach leads to the rapid synthesis of a large number of compounds within a short time-frame and facilitates their use in high throughput screening. Moreover, transferring traditional solution chemistry to the solid-phase and exploring new synthetic routes on solid support offers an opportunity for the development of novel methodologies for the construction of libraries of small heterocyclic compounds.[4-6]

1,2,4-Triazol-3-ones are a particularly attractive class of five-membered heterocyclic ring analogues for their potential anticonvulsant,[7] anti-fungal,[8] anti-inflammatory,[9] anti-tumor,[10] *in vitro* cyclooxygenase inhibition, and 5-lipoxygenase activities.[11] Recently a series of new triazolones have been synthesised as cloned mammalian Ca^{2+}-activated potassium (maxi-K) channel openers,[12] PPARs agonist[13] and NK1 antagonist[14] agents.

Substituted 1,2,4-triazol-3-ones have been successfully prepared by traditional synthesis via acylhydrazines.[15-17] All intermediates and products were obtained in required state of purity by chromatography or recrystallisation. *N*-Acylhydrazines are a versatile class of nitrogen substituted molecules with high degree of chemical reactivity, used as precursors and intermediates for many important organic molecules such as heterocycles, pharmaceuticals, polymers, dyestuffs, and photographic products.[18] In continuation of our ongoing interest in solid-phase synthesis, we have recently reported an easy method for preparation of polymer-supported acylhydrazines on Merrifield resin. We have also reported the synthesis of 1,3,4-oxadiazoline-5-thiones from resin-bound acylhydrazines.[13] To the best of our knowledge, the solid-phase synthesis of 1,2,4-triazol-3-ones has not been reported until now. Therefore, we were interested in the development of benzyl ether-linked acylhydrazine resin in which the linker group serves not only as a cleavage site of attachment for the molecule to a solid support, but also as a phenol hydroxyl-protecting group. Here we describe the solid-phase synthesis of 5-(4-hydroxyphenyl)-2,4-dihydro-1,2,4-triazol-3-ones from resin-bound acylhydrazines (Scheme 1).



Scheme 1 Synthesis of triazolones **5** *Reactants/conditions: a,* R-N=C=O (**2**), EtOH, refl; *b,* 1M Aq. NaOH, EtOH, reflux; *c,* TFA/CH_2Cl_2 (1 : 4).

Results and discussion

We prepared the polymer-supported hydrazide **1** from Merrifield resin according to our previously reported method.[19] The resin-bound acylhydrazine **1** was reacted with excess of isocyanate **2** at reflux to afford the aroylsemicarbazide resin **3**. Further the intramolecular cyclisation of the resin **3** was carried out in the presence of 1M aqueous NaOH, providing the 1,2,4-triazol-3-one resin **4** after acidification by HCl (3M). Release of the final 4,5-disubstituted 1,2,4-triazol-3-one **5** was effected by cleavage with TFA/CH_2Cl_2. The reactions appears to be quite general, both aromatic and aliphatic functionality being tolerated (Table 1).

The successful formation of resin **3** was confirmed by a comparative FT-IR study. In the IR spectrum of resin **3** several characteristic signals were present which revealed the attachment of the moiety to the resin. There were strong bands at 1685 and 1640 cm^{-1}, typical for the C=O of an aroylsemicarbazide. When the resin **3** was converted into the resin **4** the IR peak shifted to 1677 cm^{-1} corresponding to the signal for the C=O of a 1,2,4-triazol-3-one. When the resin **4** was cloven by TFA/DCM, the product **5** was obtained in good yields and high purity.

In summary, we have developed an novel solid phase synthetic route toward 1, 2, 4-triazol-3-ones from resin-bound acylhydrazines. Without column purification, 4, 5-substituted 1, 2, 4-triazol-3-ones can be obtained in good yield and high purity. We have shown that various alkyl, aryl groups can be tolerated with this method. Its simple and efficient production and the mild conditions make it invaluable for application to the automated synthesis of diverse drug-like molecules. Further work on the solid phase synthesis of heterocyclic compounds via the resin-bound acylhydrazines is under way.

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Table 1 Solid-phase synthesis of 1,2,4-triazol-3-ones **5a–h**

Entry	Product	R	Yield/%[a]	Purity/%[b]
1	**5a**	Ph	91	92
2	**5b**	2-$CH_3C_6H_4$	87	91
3	**5c**	4-$CH_3OC_6H_4$	89	93
4	**5d**	4-$CH_3C_6H_4$	94	92
5	**5e**	3-ClC_6H_4	84	90
6	**5f**	3-$CH_3C_6H_4$	86	92
7	**5g**	2,4-$F_2C_6H_3$	80	89
8	**5h**	isopropyl	86	94

[a]Yield of crude product based on the loading of acylhydrazine resin.
[b]Determined by HPLC analysis.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) spectrometer, using DMSO-d_6 as solvent and TMS internal standard. IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr. Mass spectra were obtained on a HP 5989B MS spectrometer. Microanalyses were conducted using a Carlo Erba 1106 elemental analyser. HPLC was performed on an Agilent 1100 (column, ODS 5 μm 250 × 4 mm; mobile phase, MeOH/H_2O) 75/25 (v/v); flow rate, 0.8 ml/min; detector, UV 254 nm). Samples were purified by recrystallisation for ^{13}C NMR and microanalysis.

Synthesis of compound **5a**: *typical procedure*
Resin **1**[19] (0.50 g, loading 1.59 mmol/g) and phenyl isocyanate (0.286 g, 2.4 mmol) in dry EtOH (5 ml) were heated to reflux for 4 h. After cooling, the resin was filtered off, washed with EtOH and CH_2Cl_2 to remove contaminating species, and then dried to provide the resin **3**. To a suspension of resin **3** in EtOH, aqueous NaOH (1M, 5 ml) was added. Then the mixture was heated to reflux for 10 h. After cooling, the resin was filtered off and aqueous HCl (3M, 5 ml) was added. The resin was then washed with DMF (5 ml × 3), H_2O (5 ml × 3), EtOH (5 ml × 3) and CH_2Cl_2 (5 ml × 3) to remove contaminating species, and then dried to give the resin **4**.

Resin **4** was well swollen in CH_2Cl_2 (4 ml), and TFA (1 ml) was added. The mixture was stirred at room temperature for 1 h. The mixture was filtered and the resin was washed with EtOH (5 mL × 3), then CH_2Cl_2 (5 ml × 3). The washings were combined with the filtrate, then concentrated to dryness to give the product **5a**.

5-(4-Hydroxyphenyl)-4-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-one (**5a**): M.p. 263–265°C. IR: ν_{max} 3052, 1678, 1609, 1591, 1451, 1284, 1172 cm^{-1}. NMR: δ_H 6.68 (2H, d, J = 8.4 Hz), 7.07 (2H, m), 7.24 (2H, d, J = 8.4 Hz), 7.44 (3H, m), 9.89 (1H, s), 12.00 (1H, s); δ_C 115.5, 117.9, 128.0, 128.7, 129.5, 129.5, 131.8, 134.1, 145.9, 154.8, 157.0. MS (EI, 70 eV): *m/z* 253 (M^+, 100), 210 (25), 196 (30), 134 (95), 119 (30), 107 (40), 77 (43). Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59 Found C, 66.53; H, 4.60.; N, 16.83%.

5-(4-Hydroxyphenyl)-4-(2-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5b**): M.p. 260–262°C. IR: ν_{max} 3203, 1677, 1610, 1597, 1451, 1432, 1271, 1168 cm^{-1}. NMR: δ_H 2.05 (3H, s), 6.67 (2H, d, J = 8.4 Hz), 6.83 (2H, m), 7.06 (2H, d, J = 8.4 Hz), 7.21–7.37 (2H, m), 9.90 (1H, s), 12.01 (1H, s); δ_C 17.6, 115.8, 118.2, 127.5, 128.8, 129.6, 129.8, 131.4, 133.5, 136.4, 146.0, 154.8, 159.2. MS (EI, 70 eV): 267 (M^+, 100), 250 (15), 210 (15), 135 (95), 119 (20), 107 (18), 91(35). Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found C, 67.56; H, 4.68; N, 15.67%.

5-(4-Hydroxyphenyl)-4-(4-methoxyphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5c**): M.p. 268–270°C. IR: ν_{max} 3241, 1676, 1612, 1587, 1509, 1301, 1283, 1171 cm^{-1}. NMR: δ_H 3.77 (3H, s), 6.67–6.69 (2H, d, J = 8.0 Hz), 6.98–7.00 (2H, d, J = 8.4 Hz), 7.09–7.11 (2H, d, J = 8.0 Hz), 7.15–7.17 (2H, d, J = 8.0 Hz), 9.88 (1H, s), 11.94 (1H, s); δ_C 55.7, 114.7, 115.6, 118.1, 126.8, 129.3, 129.4, 146.0, 155.1, 159.0, 159.2. MS (EI, 70 eV): *m/z* 283 (M^+, 90), 226 (15), 134 (100), 119 (20), 107 (25), 91(16). Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83; Found C, 63.86; H, 4.78; N, 14.62%.

5-(4-Hydroxyphenyl)-4-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5d**): M.p. 276–278°C. IR: ν_{max} 3245, 1672, 1605, 1592, 1415, 1311,1282, 1174 cm^{-1}. NMR: δ_H 2.33 (3H, s), 6.67–6.69 (2H, d, J = 8.4 Hz), 6.81–6.83 (2H, d, J = 8.0 Hz), 7.24 (2H, d, J = 8.4 Hz), 7.77–7.79 (2H, d, J = 8.0 Hz), 9.89 (1H, s), 11.97 (1H, s); δ_C 21.0, 115.4, 118.1, 121.6, 127.8, 130.0, 131.8, 145.9, 154.9, 159.0, 161.9. MS (EI, 70 eV): *m/z* 267 (M^+, 100), 210 (15), 134 (80), 119 (24), 107 (25), 91 (35). Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found C, 67.28; H, 5.03.; N, 15.64%.

4-(3-Chlorophenyl)-5-(4-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5e**): M.p. 276–278°C. IR: ν_{max} 3204, 1673, 1610, 1598, 1513, 1492, 1432, 1167 cm^{-1}. NMR: δ_H 6.80 (2H, d, J = 8.4 Hz), 7.04 (1H, m), 7.43 (2H, d, J = 8.4 Hz), 7.71 (2H, m), 10.02 (1H, s), 12.03 (1H, s).; δ_C 115.9, 119.8, 121.3, 123.5, 125.1, 128.1, 130.6, 134.2, 138.1, 152.2, 154.9, 159.9. MS (EI, 70 eV): *m/z* 289 (M^+ + 2, 3), 287 (M^+, 9), 153 (70), 127 (53), 121 (100). Anal. Calcd. for $C_{14}H_{10}ClN_3O_2$: C, 58.45; H, 3.50; N, 14.61. Found C, 58.67; H, 3.63; N, 14.43%.

5-(4-Hydroxyphenyl)-4-(3-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5f**): M.p. 265–267°C. IR: ν_{max} 3204, 1679, 1610, 1597, 1514, 1490, 1432, 1271, 1228, 1167 cm^{-1}. NMR: δ_H 2.30 (3H, s), 6.68 (2H, d, J = 8.4 Hz), 6.98 (1H, m), 7.10 (2H, d, J = 8.4 Hz), 7.23 (2H, m), 9.89 (1H, s), 11.99 (1H, s); δ_C 21.0, 115.5, 118.0, 125.1, 128.4, 129.3, 129.4, 134.1, 139.1, 145.8, 154.9, 159.0. MS (EI, 70 eV): *m/z* 267 (M^+, 5), 253 (100), 210 (10), 196 (35), 134 (50), 119 (60), 107 (30), 91(42).77(95). Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found C, 67.58; H, 4.83; N, 15.48%.

4-(2,4-Difluorophenyl)-5-(4-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5g**): M.p. 282–284°C. IR: ν_{max} 3214, 1676, 1610, 1597, 1514, 1490, 1432, 1167 cm^{-1}. NMR: δ_H 6.71–6.73 (2H, d, J = 8.0 Hz), 7.11–7.13 (2H, d, J = 8.0 Hz), 7.25–7.27 (1H, m), 7.61 (1H, m), 9.95 (1H, s), 12.11 (1H, s); δ_C 106.3, 115.5, 118.2, 122.4, 125.6, 126.5, 128.4, 129.9, 133.4, 139.1, 156.8, 159.4. MS (EI, 70 eV): *m/z* 287 (M^+, 9), 153 (70), 134 (100), 119 (40). Anal. Calcd. for $C_{14}H_9F_2N_3O_2$: C, 58.14; H, 3.14; N, 14.53. Found C, 57.86; H, 3.42; N, 14.46%.

5-(4-Hydroxyphenyl)-4-(1-methylethyl)-2,4-dihydro-3H-1,2,4-triazol-3-one (**5h**): M.p. 224–226°C. IR: ν_{max} 3291, 2971, 1661, 1586, 1415, 1311, 1285, 1241 cm^{-1}. NMR: δ_H 1.36 (6H, d, J = 7.2 Hz), 3.74 (1H, m). 6.89–6.91 (2H, d, J = 8.0 Hz), 7.30–7.32 (2H, d, J = 8.0 Hz), 9.87 (1H, s), 11.66 (1H, s); δ_C 20.1, 46.6, 118.3, 123.6, 130.6, 147.3, 155.2, 159.4. MS (EI, 70 eV): *m/z* 219 (M^+, 20), 176 (75), 134 (100), 119 (32), 107 (46), 91(35). Anal. Calcd. for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17; Found C, 60.43; H, 6.22; N, 19.04%.

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