Supporting Information

An Efficient and Regiospecific One-Pot Synthesis of Substituted 1,2,4-Triazoles

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Experimental section:

Reactions were performed in an open vessel unless otherwise noted. All commercially obtained reagents were used without further purification. Chromatography was performed on silica gel eluting with mixtures of either 0-10% 0.7N ammonia in methanol in ethyl acetate or 0-10% 0.7N ammonia in methanol in dichloromethane. Visualisation of triazoles during chromatography was performed either by UV at 254 nm or *via* iodine development. Melting points are uncorrected and were recorded on a Bchi B-540. ¹H and ¹³C NMR spectra were obtained from either a 300 MHz (¹H: 300 MHz, ¹³C: 75 MHz) or 400 MHz (¹H: 400 MHz, ¹³C: 100 MHz) Varian Unity Inova spectrometer. ¹H and ¹³C shifts are given in ppm., δ scale and are measured relative to tetramethylsilane as standard. Mass spectra were recorded on a Hewlett Packard HP 6890 or HP5973 MSD instrument. Microanalyses were recorded on a CE Instrument EA1110. Compounds are novel unless otherwise referenced.

Entry 1: 4-(4-Fluorobenzyl)-3,5-dimethyl-4H-1,2,4-triazole

In an open vessel, acetic hydrazide (407 mg, 5.5 mmol) was dissolved in acetonitrile (2 mL) and dimethylacetamide dimethyl acetal (732 mg, 5.5 mmol) was added. The reaction mixture was warmed to 50°C for 30 mins and then 4-fluorobenzylamine (625 mg, 5 mmol) in acetonitrile (1 mL) was added followed by acetic acid (3 mL). The reaction temperature was raised to 120°C for 3 hours, then cooled, concentrated and the residue purified by chromatography on silica gel eluting initially with ethyl acetate followed by 5% 0.7N ammonia in methanol in ethyl acetate to afford 4-(4-fluorobenzyl)-3,5-dimethyl-4H-1,2,4-triazole (702 mg, 69%) as a white solid after triturating with diethyl ether.

Mpt. 76-77°C. MS(APCI +ve) 206 (M+H).

Microanalysis: found (expected) C 64.41 (64.38); H 5.87 (5.89); N 20.14 (20.47)

¹H nmr, CDCl₃, 300 MHz δ 7.09-7.02 (2H, m); 6.99-6.94 (2H, m); 5.0 (2H, s); 2.35 (6H, s) ppm.

¹³C nmr, CDCl₃ 75 MHz δ 162.5 (d, J=254Hz); 151.4; 130.2; 127.7 (d, J=8.3Hz); 116.3 (d, J=22.1Hz); 46.1, 11.0 ppm.

Entry 2: 4-(4-Fluorobenzyl)-3-methyl-4H-1,2,4-triazole

Prepared in 68% yield as an oil:

MS(APCI +ve) 192 (M+H)

¹H nmr, CDCl₃, 400 MHz δ 8.08 (1H, s); 7.12-7.06 (4H, m); 5.06 (2H, s); 2.38 (3H, s) ppm.

^{13}C nmr, CDCl_3 75 MHz δ 162.5 (d, $J=297\text{Hz}$); 150.7; 143.1; 130.0; 128.8 (d, $J=8.2\text{Hz}$); 116.4 (d, $J=21.4\text{ Hz}$); 47.5; 10.4 ppm.

Entry 3: 4-Benzyl-3-methyl-4H-1,2,4-triazole

Prepared in 39% yield as a white solid:

Mpt. 66-69°C. MS(APCI +ve) 174 (M+H)

^1H nmr, CDCl_3 , 300MHz δ 8.09 (1H, s); 7.40-7.33 (3H, m); 7.12-7.09 (2H, m); 5.08 (2H, s); 2.39 (3H, s) ppm.

^{13}C nmr, CDCl_3 75MHz δ 151.0; 143.7; 134.3; 129.3; 128.7; 126.9; 48.1; 10.4 ppm.

Entry 4: 4-Methoxybenzyl-3-methyl-4H-1,2,4-triazole

Prepared in 22% yield as a white solid:

Mpt. 88-90°C. MS(APCI +ve) 204 (M+H)

^1H nmr, CDCl_3 , 300MHz δ 8.04 (1H, s); 7.05 (2H, dd, $J=8.8, 2\text{Hz}$); 6.90 (2H, dd, $J=8.8, 2\text{Hz}$); 5.00 (2H, s); 3.81 (3H, s); 2.39 (3H, s) ppm.

^{13}C nmr, CDCl_3 75MHz δ 159.8; 150.9; 143.6; 128.6; 126.1; 114.6; 55.4; 47.8; 10.5 ppm.

Entry 5: 4-Nitrobenzyl-3-methyl-4H-1,2,4-triazole

Prepared in 48% yield as a yellow solid:

Mpt. 170-171 °C. MS(APCI +ve) 219 (M+H)

Microanalysis: found (expected) C 54.84 (55.04); H 4.67 (4.62); N 25.62 (25.68)

^1H nmr, CDCl_3 , 300MHz δ 8.27-8.25 (2H, d, $J=6.8\text{Hz}$); 8.15 (1H, s); 7.26-7.24 (2H, d, $J=6.8\text{Hz}$); 5.22 (2H, s); 2.39 (3H, s) ppm.

^{13}C nmr, CDCl_3 75MHz δ 150.9; 148.1; 143.8; 141.4; 127.5; 124.5; 47.2; 10.4 ppm.

Entry 6: 3-Methyl-4-phenyl-4H-1,2,4-triazole

Ried, W. and Lohwasser, H. *Justus Liebigs Ann. Chem.* **1966**, 699, 88-97.

Prepared in 64% yield as a white solid:

Mpt. 102-103°C. MS(APCI +ve) 160 (M+H)

^1H nmr, CDCl_3 , 300 MHz δ 8.22 (1H, s); 7.60-7.49 (3H, m); 7.32-7.28 (2H, m); 2.44 (3H, s) ppm.

^{13}C nmr, CDCl_3 100 MHz δ 150.8; 143.4; 134.0; 130.0; 129.5; 125.3; 10.8 ppm.

Entry 7: 3,5-Dimethyl-4-phenyl-4H-1,2,4-triazole

Ried, W. and Lohwasser, H. *Justus Liebigs Ann. Chem.* **1966**, 699 88-97.

Prepared in 55% yield as a white solid:

Mpt. 241-242°C. MS(APCI +ve) 174 (M+H)

Microanalysis: found (expected) C 69.31 (69.34); H 6.53 (5.40); N 24.14 (24.26)

¹H nmr, CDCl₃, 400 MHz δ 7.60-7.52 (3H, m); 7.22-7.17 (2H, m); 2.62 (6H, s) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 151.4; 133.8; 130.1; 129.7; 126.8; 11.2 ppm.

Entry 8: 4-(4-Methoxyphenyl)-3-methyl-4H-1,2,4-triazole

Heeres, J.; Backx, L. J. J. and Mostmans, J. H. DE2803870 **1978** [*Chem. Abst.* **1978**, 90, 6400].

Prepared in 87% yield as a white solid:

Mpt. 112-113°C. MS(APCI +ve) 190 (M+H)

Microanalysis: found (expected) C 63.27 (63.48); H 5.84 (5.86); N 22.50 (22.21)

¹H nmr, CDCl₃, 300 MHz δ 8.16 (1H, s); 7.22-7.19 (2H, m); 7.04-7.01 (2H, m); 3.88 (3H, s); 2.39 (3H, s) ppm.

¹³C nmr, CDCl₃ 75 MHz δ 160.2; 151.2; 143.7; 126.7; 126.7; 115.0; 55.6; 10.6 ppm.

Entry 9: 4-(4-Methoxyphenyl)-3,5-dimethyl-4H-1,2,4-triazole

Benkhoud, M. L. and Baccar, B. J. *de la Societe Chimique de Tunisie* **1991**, 3(1), 3-10.

Prepared in 60% yield as a white solid:

Mpt. 177-178°C. MS(APCI +ve) 204 (M+H)

Microanalysis: found (expected) C 64.77 (65.01); H 6.49 (6.45); N 20.58 (20.67)

¹H nmr, CDCl₃, 400 MHz δ 7.11 (2H, d, J=2.4Hz); 7.10 (2H, d, J=2.4Hz); 3.89 (3H, s); 2.25 (6H, s) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 160.6; 151.6; 127.9; 126.2; 115.0; 55.6; 11.2 ppm.

Entry 10: Ethyl 4-(3-methyl-4H-1,2,4-triazol-4-yl)benzoate

Prepared in 43% yield as a white solid:

Mpt. 103-104°C. MS(APCI +ve) 232(M+H)

Microanalysis: found (expected) C 62.09 (62.33); H 5.69 (5.67); N 17.91 (18.17)

¹H nmr, CDCl₃, 400 MHz δ 8.23 (2H, dd, J=2 and 8.4Hz); 8.22 (1H, s); 7.39 (2H, dd, J= 2 and 8.4Hz); 4.44 (2H, q, J = 7.2Hz); 2.47 (3H, s); 1.43 (3H, t, J = 7.2Hz) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 165.1; 150.5; 143.0; 137.6; 131.5; 131.4; 125.0; 61.6; 14.3; 10.9 ppm.

Entry 11: 4-(4-Fluorobenzyl)-3-(4-methylphenyl)-4H-1,2,4-triazole

Prepared in 65% yield as a white solid:

Mpt. 125-127°C. MS (APCI +ve) 268 (M+H)

¹H nmr, CDCl₃, 400 MHz δ 8.15 (1H, s); 7.45 (2H, d, J=8Hz); 7.28 (2H, d, J = 4.4Hz); 7.08-7.02 (4H, m); 5.18 (2H, s); 2.41 (3H, s) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 162.4 (d, J = 290Hz); 154.5; 144.3; 140.5; 130.8; 129.6; 128.8; 128.7; 123.6; 116.3 (d, J=21.5Hz); 48.0; 21.4 ppm.

Entry 12: 4-(4-Fluorobenzyl)-3-(4-methoxyphenyl)-4H-1,2,4-triazole

Prepared in 33% yield as a white solid:

Mpt. 77-78°C. MS (APCI +ve) 284 (M+H)

Microanalysis: found (expected) C 67.78 (67.83); H 5.06 (4.98); N 14.92 (14.83)

¹H nmr, CDCl₃, 300 MHz δ 8.15 (1H, s); 7.50 (2H, d, J= 9.3Hz); 7.05 (4H, d, J = 6.9 Hz); 6.96 (2H, d, J=9.3Hz); 5.17 (2H, s); 3.85 (3H, s) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 162.7 (d, J = 227Hz); 161.0; 153.7; 144.2; 131.1; 130.3; 128.7 (d, J=7.6Hz); 118.7; 116.3 (d, J=21.4Hz); 114.4; 55.4; 48.0 ppm.

Entry 13: 4-(4-Fluorobenzyl)-3-(4-nitrophenyl)-4H-1,2,4-triazole

Prepared in 51% yield as a white solid:

Mpt. 150-151°C. MS (APCI +ve) 299 (M+H)

¹H nmr, CDCl₃, 300 MHz δ 8.81 (1H, s); 8.30 (2H, d, J=9Hz); 7.93 (2H, d, J=9Hz); 7.17-7.08 (4H, m); 5.46 (2H, s) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 161.6 (d, J=244Hz); 151.4; 148.0; 133.2; 131.9; 129.7; 129.4; 123.4; 129.3; 115.7 (d, J=22.2Hz); 47.4 ppm.

Entry 14: 4-[(3-Methyl-4H-1,2,4-triazol-4-yl)methyl]pyridine

Prepared in 42% yield as a yellow solid:

Mpt. 90-93°C. MS(EI) 174(M+)

Microanalysis: found (expected) C 60.10 (62.05); H 5.86 (5.79); N 30.92 (32.16)

¹H nmr, CDCl₃, 300MHz δ 8.65-8.64 (2H, m); 8.15 (1H, s); 6.98-6.97 (2H, m); 5.14 (2H, s); 2.38 (3H, s) ppm.

¹³C nmr, CDCl₃ 100MHz δ 151.0; 150.7; 143.8; 143.4; 121.1; 46.7; 10.2 ppm.

Entry 15: 4-Allyl-3-methyl-4H-1,2,4-triazole

Prepared in 56% yield as a colourless oil:

MS(EI) 123 (M+)

¹H nmr, CDCl₃, 300MHz δ 8.06 (1H, s); 5.91 (1H, dddd, J=16.4, 9.2, 3.6, 1.6Hz); 5.34 (1H, dd, J=9.2, 1.2Hz); 5.09 (1H, dd, J=16.4, 1.2Hz); 4.51 (2H, dd, J=3.6, 1.6Hz); 2.43 (3H, s) ppm.

¹³C nmr, CDCl₃ 75MHz δ 150.9; 143.4; 131.1; 119.0; 46.6; 10.2 ppm.

Entry 16: 3-Methyl-4-prop-2-yn-1-yl-4H-1,2,4-triazole

Prepared in 13% yield as a yellow oil:

MS(EI) 121 (M+)

¹H nmr, CDCl₃, 300MHz δ 8.19 (1H, s); 4.67-4.66 (2H, m); 2.54-2.51 (3H, m); 1.75 (1H, s) ppm.

¹³C nmr, CDCl₃ 75MHz δ 150.5; 143.0; 75.5; 75.0; 34.1; 10.2 ppm.

Entry 17: 4-Cyclohexyl-3-methyl-4H-1,2,4-triazole

Prepared in 9% yield as a white solid:

Mpt. 100-101°C. MS (EI) 165 (M+)

Microanalysis: found (expected) C 65.26 (65.42); H 9.16 (9.15); N 25.44 (25.43)

¹H nmr, CDCl₃, 300 MHz δ 8.12 (1H, s); 3.84-3.76 (1H, m); 2.46 (3H, s); 2.08-2.04 (2H, m); 1.98-1.93 (2H, m); 1.82-1.77 (1H, m); 1.67-1.55 (2H, m); 1.49-1.38 (2H, m); 1.33-1.21 (1H, m) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 149.5; 140.3; 54.9; 33.9; 25.5; 24.9; 10.7 ppm.

Entry 18: 4-Cyclohexyl-3-(4-methylphenyl)-4*H*-1,2,4-triazole

Prepared in 13% yield as a white solid:

Mpt. 125-126°C. MS (APCI +ve) 242 (M+H)

Microanalysis: found (expected) C 74.65 (74.01); H 7.94 (7.93); N 17.41(17.01)

¹H nmr, CDCl₃, 400 MHz δ 8.30 (1H, s); 7.45 (2H, d, J=8Hz); 7.32 (2H, d, J=8Hz); 4.06-3.98 (1H, m); 2.44 (3H, s); 2.08-2.04 (2H, m); 1.98-1.93 (2H, m); 1.79-1.60 (3H, m); 1.38-1.23 (3H, m) ppm.

¹³C nmr, CDCl₃ 100 MHz δ 153.6; 141.2; 140.1; 129.6; 128.8; 124.4; 55.0; 34.6; 25.4; 24.9; 21.4 ppm.

***N'*-Acetyl-*N,N*-dimethylhydrazonoformamide**

In an open vessel, acetic hydrazide (407 mg, 5.5 mmol) was dissolved in acetonitrile (2 mL) and dimethylacetamide dimethyl acetal (732 mg, 5.5 mmol) added. The reaction mixture was warmed to 50°C for 30 mins and then concentrated. The resulting residue was purified on silica gel eluting with 5% of 0.7N ammonia in methanol in dichloromethane to afford *N'*-Acetyl-*N,N*-dimethylhydrazonoformamide (590 mg, 91%) as a white solid.

Mpt. 143-144°C. MS (APCI +ve) 130.2 (M+H)

¹H nmr, DMSO, 300 MHz mixture of 2 diastereomers δ 9.92 (1H, br); 9.67 (1H, br); 7.67 and 7.51 (1H, 2s); 2.76 and 2.73 (6H, 2s); 1.92 and 1.75 (3H, 2s) ppm.

¹³C nmr, DMSO 100 MHz mixture of 2 diastereomers δ 169.4 and 169.0 (2xq); 167.9 and 163.9 (2xq); 154.3 and 148.2 (2xCH); 40.1 and 39.8 (2xCH₃); 21.4 and 20.4 (2xCH₃) ppm.