Microwave-assisted synthesis of substituted 1,2,4-triazoles

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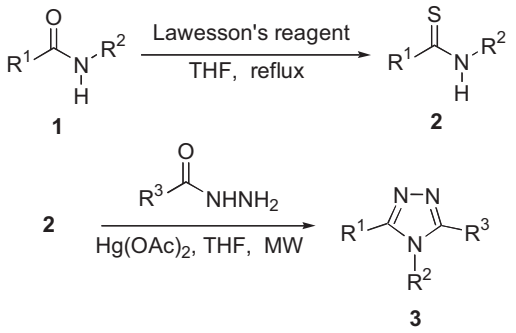
An efficient synthesis of substituted 1,2,4-triazoles has been extended, utilising a wide range of *N*-substituted amides and hydrazides

Keywords: microwave, 1,2,4-triazoles, Lawesson's reagent, hydrazines

The 1,2,4-triazole as a constituent moiety of several biologically active therapeutics is present in certain anti-asthmatic,[1] antiviral,[2] antifungal,[3] antibacterial,[4] and hypnotic[5] drugs. Owing to its broad spectrum of biological activity,[6-12] the 1,2,4-triazole ring system has attracted much attention.

Many methods have been investigated for the synthesis of such heterocycles,[13-17] but the most explored strategy involves cyclisation of an acylamidrazone intermediate.[18-20] Recently, the application of microwave (MW) irradiation in organic synthesis has been the focus of considerable attention and is becoming an increasingly popular technology,[21] owing to the rapid reaction rates, clean reaction conditions and ease of manipulation.

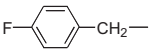
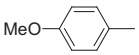
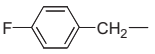
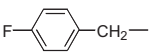
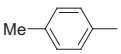
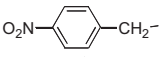
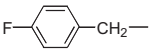
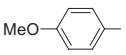
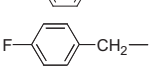
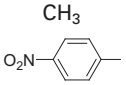
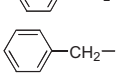
Hitostuyanagi's group[22] has recently reported the preparation of 1,2,4-triazole derivatives, starting from Boc-thionotripeptides, but performing cyclisation only with formic hydrazide. This reaction is very attractive, owing to the mild reaction conditions used for the heterocycle formation, which contained the condensation of a thionotripeptide with an excess of formic hydrazide at room temperature in the presence of mercury(II) acetate. In order to extend the synthetic scope and the functional group tolerance of this reaction, we wished to explore this route for the synthesis of 1,2,4-triazole derivatives starting from thioamides,[23] prepared from amides and Lawesson's reagent, and various benzoylhydrazines.



Scheme 1

The synthetic route described in Scheme 1 was utilised for the synthesis of 1,2,4-triazoles. Initially, amides were treated with Lawesson's reagent in THF to obtain the corresponding thioamides, which were subjected to microwave heating with 1.2 equiv of hydrazine and 1.2 equiv of $Hg(OAc)_2$ in THF to obtain 1,2,4-triazoles.[3] The completion of this step was monitored by TLC (observing the disappearance of thioamides). After purification by column chromatography, the desired compounds were obtained in 65–90 % yield (Table 1). All compounds were confirmed NMR and MS.

Table 1 Synthesis of 1,2,4-triazoles from thioamides and hydrazine under microwave irradiation

Compound	R^1	R^2	R^3	Yield/ %*	M.p./°C	Lit. m.p./°C
3a	CH_3		CH_3	85	78–80	(76–77)[16]
3b	H_3C–		H_3C–	82	247–249	(236)[24]
3c	H_3C–		H_3C–	83	195–196	–
3d	H		CH_3	87	Liquid	(oil)[16]
3e	H			81	127–129	(125–127)[16]
3f	H		CH_3	65	169–170	(170–171)[16]
3g	H		CH_3	78	103–104	(100–101)[16]
3h	H			89	75–76	(77–78)[16]
3i	H		CH_3	77	102–103	(102–103)[16]
3j	H			78	144–145	(150–151)[16]
3k	H		CH_3	90	67–69	(66–69)[16]

*Yields refer to the isolated products.

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Using the optimised conditions, a variety of 1,2,4-triazoles were synthesised. As reported in Table 1, the expected compounds were obtained in high yield. However, when both positions 4 and 5 of the triazoles are benzene rings, the yields of the compounds were very low. It is easy to understand, since two adjacent aryl groups may increase the steric hindrance. We attempted to prolong the reaction time to make it proceed, but the predicted results were not obtained. Therefore, we suppose that the steric hindrance is an important factor. In fact, we have initially wanted to synthesise 3,4,5-triaryl-substituted-1,2,4-triazoles. When these experiments failed, our aim was transferred to aliphatic amides or aliphatic acids.

In conclusion: we have developed a novel method for the synthesis of 1,2,4-triazoles derivatives. The successful synthesis for the target compounds demonstrates that this strategy may provide a useful tool for the synthesis of new scaffolds containing trisubstituted triazoles and allow preparation of triazole libraries.

Experimental

All the reagents were commercially available. NMR spectra were on a Bruker AM-400 spectrometre using $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded on a QP-1000A GC-MS using the EI mode (70eV). Elemental analyses were performed on a Vario El elemental analysis instrument. Melting points were determined with an electrothermal micromelting point apparatus.

Typical procedure for preparation of **3a–k**:
$Hg(OAc)_2$ (1 mmol) was added to thioamide (1 mmol) and hydrazide (1 mmol) in THF (20 ml) in a flask, and the mixture was stirred 10 minutes and placed inside a large container filled with alumina at the centre of a domestic microwave oven. After irradiation at 490 W for the necessary time (the reaction was monitored by TLC) After the reaction was complete the mixture was cooled to r.t. and filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc, and then the solution was washed with dilute hydrochloric acid and saturated sodium chloride solution, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant compound was purified by column chromatography to give the 1,2,4-triazole derivatives. Analytical samples were obtained by column chromatography. The data for compounds **3a–k** are given below:

*4-(4-Fluorobenzyl)-3,5-dimethyl-4H-1,2,4-triazol*e (**3a**): ^{1}H NMR (400 MHz): δ 7.08–7.02 (2H, m), 6.99–6.95 (2H, m), 5.01 (2H, s), 2.36 (6H, s).^{13}C NMR (100 MHz): δ 162.3, 151.6, 131.3, 127.7, 116.5, 46.6, 11.0.

3,5-Dimethyl-4-phenyl-4H-1,2,4-triazole (**3b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.51 (3H, m); 7.22–7.16 (2H, m); 2.63 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 152.3; 135.6; 132.3; 130.5; 127.8; 11.6.

4-(4-Methoxyphenyl)-3,5-dimethyl-4H-1,2,4-triazole (**3c**): ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (4H, m); 3.90 (3H, s); 2.24 (6H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 161.5; 151.6; 128.1; 127.2; 115.0; 55.6; 11.4. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.02; H, 6.60; N, 20.59.

4-(4-Fluorobenzyl)-3-methyl-4H-1,2,4-triazole (**3d**): ^{1}H NMR (400 MHz): δ 8.08 (1H, s), 7.11–7.06 (4H, m), 5.04 (2H, s), 2.37 (3H, s). ^{13}C NMR (100 MHz): δ 162.4, 150.4, 143.3, 130.8, 128.5, 115.9, 47.7, 10.2.

4-(4-Fluorobenzyl)-3-(4-methylphenyl)-4H-1,2,4-triazole (**3e**): ^{1}H NMR (400 MHz): δ 8.14 (1H, s), 7.48 (2H, d), 7.30 (2H, d), 7.10–7.03 (4H, m), 5.20 (2H, s), 2.39 (3H, s). ^{13}C NMR (100 MHz): δ 162.8, 155.1, 143.9, 140.6, 130.8, 129.5, 129.1, 124.1, 116.3, 48.3, 21.6.

4-Nitrobenzyl-3-methyl-4H-1,2,4-triazole (**3f**): ^{1}H NMR (400 MHz): δ 8.26–8.24 (2H, d), 8.15 (1H, s), 7.28–7.25 (2H, d), 5.24 (2H, s), 2.39 (3H, s). ^{13}C NMR (100 MHz): δ 151.4, 147.8, 143.5, 141.1, 127.5, 125.0, 46.9, 10.5.

4-Cyclohexyl-3-methyl-4H-1,2,4-triazole (**3g**): ^{1}H NMR (400 MHz): δ 8.13 (1H, s), 3.82–3.77 (1H, m), 2.48 (3H, s), 2.07–1.94(4H, m), 1.84–1.76 (1H, m), 1.66–1.53 (2H, m), 1.50–1.40 (2H, m), 1.35–1.24 (1H, m). ^{13}C NMR (100 MHz): δ 150.0, 140.2, 54.8, 34.0, 25.5, 24.8, 10.5.

4-(4-Fluorobenzyl)-3-(4-methoxyphenyl)-4H-1,2,4-triazole (**3h**): ^{1}H NMR (400 MHz): δ 8.16 (1H, s), 7.54 (2H, d), 7.07 (4H, d), 6.99 (2H, d), 5.18 (2H, s), 3.87 (3H, s). ^{13}C NMR (100 MHz): δ 162.8, 161.8, 154.7, 144.6, 132.0, 129.7, 128.8, 119.1, 116.5, 115.0, 55.2, 48.3.

3-Methyl-4-phenyl-4H-1,2,4-triazole (**3i**): ^{1}H NMR (400 MHz): δ 8.20 (1H, s), 7.60–7.50 (3H, m), 7.32–7.29 (2H, m), 2.42 (3H, s). ^{13}C NMR (100 MHz): δ 151.0, 143.1, 134.0, 130.1, 130.0, 126.0, 10.8.

4-(4-Fluorobenzyl)-3-(4-nitrophenyl)-4H-1,2,4-triazole (**3j**): ^{1}H NMR (400 MHz): δ 8.78 (1H, s), 8.31 (2H, d), 7.94 (2H, d), 7.16–7.10 (4H, m), 5.48 (2H, s).^{13}C NMR (100 MHz): δ 161.8, 151.3, 148.1, 133.6, 132.0, 130.4, 129.4, 123.4, 116.0, 47.4.

4-Benzyl-3-methyl-4H-1,2,4-triazole (**3k**): ^{1}H NMR (400 MHz); δ 8.10 (1H, s), 7.40–7.34 (3H, m), 7.12–7.10 (2H, m), 5.08 (2H, s), 2.40 (3H. s). ^{13}C NMR (100 MHz): δ 151.2, 143.9, 134.5, 129.5, 128.6, 127.9, 48.1, 10.5.

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