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MICROWAVE-ASSISTED AND EFFICIENT ONE-POT SYNTHESIS OF SUBSTITUTED 1,2,4-TRIAZOLES

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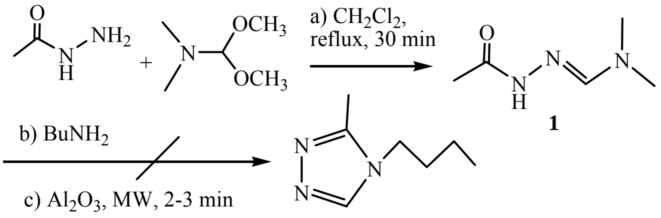
Abstract –An efficient microwave-assisted one-pot and three-component synthesis of substituted 1,2,4-triazoles has been achieved utilizing substituted primary amines.

INTRODUCTION

1,2,4-Triazoles are attractive constructs because of their unique chemical properties and structure. They have been found many applications in organic, organometallic, and medicinal chemistry, as well as in materials chemistry and biology.[1] As a consequence, a number of synthetic methods have been developed to construct this ring system.[1, 2] The three-component procedure developed by Stocks[3] was the first one-pot synthesis reported for preparation of 1,2,4-triazoles, though it provided an efficient procedure and the possible reaction pathway to prepare 1,2,4-triazoles. There remains a drawback of low yield in the synthesis of 4-alkyl-substituted 1,2,4-triazoles. As well-known, microwave induced has emerged as a powerful technique to promote a variety of organic reactions under solvent-free conditions offering reduced pollution and low cost together with simplicity in processing and handling.[4] These promote us to carry out this one-pot, three-component reaction with microwave assisted.

RESULTS AND DISCUSSION

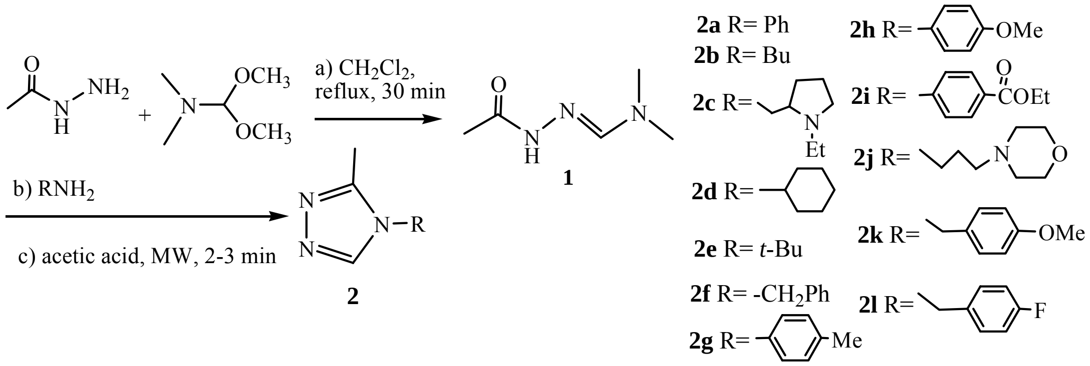
In our initial studies, *N'*-acetyl-*N,N*-dimethylhydrazonoformamide (**1**) was generated by combining acetic hydrazide with DMF-DMA(dimethylformamide dimethylacetal) in CH_2Cl_2 under refluxing(**Scheme 1**); then acidic Al_2O_3 was used as a carrier and was catalyst in the acid-catalyzed ring closure step.[5] However, no desired product was obtained under microwave irradiation.



Scheme 1 Initial Results Employing Butylamine with MW

Since the desired products were not obtained under solvent-free condition, acetic acid was used as solvent also as catalyst instead of acidic Al_2O_3. The mixture reacted under microwave irradiation for 2-3 min to prepare the substituted 1,2,4-triazoles. Fortunately, satisfactory results were obtained (**Table 1**).

Table 1 Microwave-assisted one-pot synthesis of substituted 1,2,4-triazoles



Entry	R-NH_2	Product	Yield(%)	Yield(%)[a]
1	aniline	**2a**	77	64
2	butylamine	**2b**	68	/
3	2-aminomethyl-1-ethylpyrrolidine	**2c**	95	/
4	cyclohexylamine	**2d**	72	52[b]
5	*tert*-butylamine	**2e**	66	/
6	benzylamine	**2f**	81	39
7	4-methylaniline	**2g**	98	/
8	4-methoxyaniline	**2h**	97	87
9	ethyl 4-aminobenzoate	**2i**	55	43
10	*N*-(3-aminopropyl)morpholine	**2j**	98	/
11	4-methoxybenzylamine	**2k**	72	22
12	4-fluorobenzylamine	**2l**	82	68

Note: [a] This yield was provided by reference 3. [b] This yield was achieved by using *N*-dimethoxymethyl-*N*,*N'*,*N'*-trimethylethane-1,2-diamine instead of DMF-DMA.

Our microwave-assisted procedure is more efficient than that without microwave-assisted with higher yield and shorter reaction time.

EXPERIMENTAL

Melting points were determined with an XT-4 apparatus and were uncorrected. The ^{1}HNMR spectra were measured with BRUKER AV-300 spectrometers.

General Prcedure for the synthesis of substituted 1,2,4-triazoles:

In an open vessel (25 mL), acetic hydrazide (222 mg, 3 mmol) was dissolved in dichloromethane (2 mL) and dimethylformamide dimethyl acetal (3 mmol) was added. The reaction mixture was refluxing for 30 min, evaporated in vacuo and RNH_2 (2.8 mmol) was added followed by acetic acid (1.5 mL). The reaction mixture was standed under microwave irradiation for 2-3 min, then cooled, concentrated and the residue was purified by chromatography on silica gel.(Eluent: MeOH: Ethyl Acetate=20:1 to MeOH: Ethyl Acetate=1:1).

Entry 1: 3-Methyl-4-phenyl-1,2,4-triazole (2a)[3]

Prepare in 77% yield as a white solid. mp 101-103°C, 102-103 °C(lit.). ^{1}HNMR($CDCl_3$, 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}CNMR($CDCl_3$, 75 MHz) δ: 150.5, 143.2, 134.1, 130.0, 129.4, 125.3, 10.7 ppm; HRMS(EI): $C_9H_9N_3$, calcd: 159.0796, find: 159.0793.

Entry 2: 4-Butyl-3-methyl-1,2,4-triazole (2b)

Prepare in 68% yield as yellow oil. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.05(1H, s), 3.89(2H, t, J=7.1 Hz), 2.49(3H, s), 1.74(2H, m), 1.38(2H, m), 0.95(3H, t, J=7.2 Hz) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 150.3, 143.1, 44.2, 32.4, 19.7, 13.6, 10.3 ppm; HRMS(EI): $C_7H_{13}N_3$, calcd: 139.1109, find: 139.1116; Anal. Calcd for $C_7H_{13}N_3$ C, 60.40; H, 9.41; N, 30.19. Found: C, 60.07; H, 9.65; N, 29.98.

Entry 3: 1-Ethyl-2-(3-methyl-1,2,4-triazole-4-methyl)pyrrolidine (2c)

Prepare in 95% yield as yellow oil. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.22(1H, s), 3.95(2H, d, J=5.5 Hz), 3.19(1H, t, J=6.9 Hz), 2.78(1H, m), 2.63(1H, m), 2.48(3H, s), 2.25-2.41(2H, m), 1.89(1H, m), 1.58-1.80(2H, m), 1.48(1H, m), 1.07(3H, t, J=7.1 Hz) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 151.0, 144.0, 63.5, 53.5, 49.3, 48.0, 28.7, 23.2, 21.5, 13.8, 10.6 ppm; HRMS(EI): $C_{10}H_{18}N_4$, calcd: 194.1531, find: 194.1526; Anal. Calcd for $C_{10}H_{18}N_4$ C, 61.82; H, 9.34; N, 28.84. Found: C, 61.49; H, 9.54; N, 28.62.

Entry 4: 4-Cyclohexyl-3-methyl-1,2,4-triazole (2d)[3]

Prepare in 72% yield as a white solid. mp 99-100°C, 100-101°C(lit.). ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.15(1H, s), 3.86(1H, m), 2.48(3H, s), 2.08-2.04(2H, m), 1.98-1.93(2H, m), 1.82-1.77(1H, m), 1.68-1.59(2H, m), 1.55-1.43(2H, m), 1.38-1.26(1H, m) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 150.0, 140.4, 54.8, 33.7, 25.3, 24.8, 10.5 ppm; HRMS(EI): $C_9H_{15}N_3$, calcd: 165.1266, find: 165.1260.

Entry 5: 4-*tert*-Butyl-3-methyl-1,2,4-triazole (2e)

Prepare in 66% yield as a white solid. mp 90-92°C. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.16(1H, s), 2.63(3H, s), 1.65(9H, s) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 150.2, 141.6, 56.0, 29.9, 14.1 ppm; HRMS(EI): $C_7H_{13}N_3$, calcd: 139.1109, find: 139.1118; Anal. Calcd for $C_7H_{13}N_3$ C, 60.40; H, 9.41; N, 30.19. Found: C, 60.11; H, 9.61; N, 29.92.

Entry 6: 4-Benzyl-3-methyl-1,2,4-triazole (2f)[3]

Prepare in 81% yield as a white solid. mp 65-67°C, 66-69°C(lit.). ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.10(1H, s), 7.40-7.33(3H, m), 7.12-7.09(2H, m), 5.10(2H, s), 2.37(3H, s) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 151.0, 143.7, 134.3, 129.3, 128.6, 127.0, 48.1, 10.4 ppm; HRMS(EI): $C_{10}H_{11}N_3$, calcd: 173.0953, find: 173.0952.

Entry 7: 3-Methyl-4-(4-methylphenyl)-1,2,4-triazole (2g)

Prepare in 98% yield as a white solid. mp 42-44°C. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.22(1H, s), 7.35(2H, d, J=8.0 Hz), 7.18(2H, d, J=8.0 Hz), 2.47(3H, s), 2.43(3H, s) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 151.0, 143.5, 139.9, 131.4, 130.6, 125.2, 21.3, 21.2, 10.7 ppm; HRMS(EI): $C_{10}H_{11}N_3$, calcd: 173.0953, find: 173.0944; Anal. Calcd for $C_{10}H_{11}N_3$ C, 69.34; H, 6.40; N, 24.26. Found: C, 69.01; H, 6.59; N, 23.95.

Entry 8: 4-(4-Methoxyphenyl)-3-methyl-1,2,4-triazole (2h)[3]

Prepare in 97% yield as a white solid. mp 110-111°C, 112-113°C(lit.). ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.21(1H, s), 7.25(2H, dd, J=2.0, 4.6 Hz), 7.05 (2H, dd, J=2.0, 4.6 Hz), 3.90(3H, s), 2.42(3H, s) ppm; ^{13}CNMR($CDCl_3$, 75M Hz) δ: 160.4, 151.2, 143.6, 126.8, 126.5, 115.1, 55.6, 10.6 ppm; HRMS(EI): $C_{10}H_{11}N_3O$, calcd: 189.0902, find: 189.0908.

Entry 9: Ethyl 4-(3-methyl-1,2,4-triazole-4-yl)benzoate (2i)[3]

Prepare in 55% yield as a white solid. mp 101-102°C, 103-104 °C(lit.). ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.28(1H, s), 8.24(2H, dd, J=2.0, 8.4 Hz), 7.44(2H, dd, J=2.0, 8.4 Hz), 4.44(2H, q, J=7.2 Hz), 2.48(3H, s), 1.43(3H, t, J=7.2 Hz) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 165.0, 150.4, 143.0, 137.6, 131.4, 125.1, 61.6, 14.3, 10.9 ppm; HRMS(EI): $C_{12}H_{13}N_3O_2$, calcd: 231.1008, find: 231.1002.

Entry 10: 4-(3-*N*-Morpholine-propyl)-3-methyl-1,2,4-triazole (2j)

Prepare in 98% yield as yellow oil. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.15(1H, s), 4.01(2H, t, J=6.9 Hz), 3.74-3.70(4H, m), 2.48-2.44(7H, m), 2.33(2H, t, J=6.5 Hz), 2.00-1.91(2H, m) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 150.7, 143.4, 66.5, 54.1, 53.2, 41.8, 26.2, 10.0 ppm; HRMS(EI): $C_{10}H_{18}N_4O$, calcd: 210.1481, find: 210.1484; Anal. Calcd for $C_{10}H_{18}N_4O$ C, 57.12; H, 8.63; N, 26.64. Found: C, 56.80; H, 8.77; N, 26.37.

Entry 11: 4-(4-Methoxybenzyl)-3-methyl-1,2,4-triazole (2k)[3]

Prepare in 72% yield as a white solid. mp 86-88°C, 88-90°C(lit.). ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.07(1H, s), 7.05(2H, dd, J= 8.8, 2.0 Hz), 6.90(2H, dd, J= 8.8, 2.0 Hz), 5.02(2H, s), 3.80(2H, s), 2.38(3H, s) ppm; ^{13}CNMR($CDCl_3$, 75 MHz) δ: 159.8, 150.9, 143.5, 128.7, 126.0, 114.6, 55.3, 47.8, 10.3 ppm; HRMS(EI): $C_{11}H_{13}N_3O$, calcd: 203.1059, find: 203.1061.

Entry 12: 4-(4-Fluorobenzyl)-3-methyl-1,2,4-triazole (2l)[3]

Prepare in 82% yield as an oil. ^{1}HNMR($CDCl_3$, 300 MHz) δ: 8.09(1H, s), 7.12-7.06(4H, m), 5.10(2H, s), 2.37(3H, s) ppm; ^{13}CNMR($CDCl_3$, 75MHz) δ: 164.4, 161.1, 150.8, 143.6, 130.2, 128.9(d, J=8.3 Hz), 116.4(d, J=21.8 Hz), 47.5, 10.4 ppm; HRMS(EI): $C_{10}H_{10}N_3F$, calcd: 191.0859, find: 191.0857.

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