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HIGH-THROUGHPUT SYNTHESIS OF SYMMETRICALLY 3,5-DISUBSTITUTED 4-AMINO-1,2,4-TRIAZOLES FROM ALDEHYDES USING MICROWAVE

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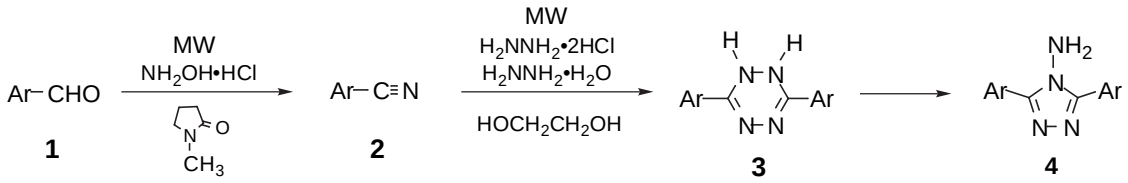
Abstract - Symmetrically 3,5-substituted 4-amino-1,2,4-triazoles are quickly prepared from aromatic aldehydes *via* nitriles by two-step reactions without any separation under microwave irradiation for each several minutes.

In rapid synthesis, it is necessary to decrease the reaction time as well as simplify the separation procedures. Use of microwave heating brings the technical solutions because of dramatic decrease of reaction time.[1-3] 4-Aminotriazoles are potentially good corrosion inhibitors for metals.[4,5] Symmetrically 3,5-disubstituted 4-amino-1,2,4-triazoles (**4**) are prepared by one-step reaction of aromatic nitriles (**2**) *via* dihydrotetrazines (**3**) with hydrazine dihydrochloride in the presence of an excess of hydrazine hydrate in ethylene glycol.[6] Microwave heating shortens the reaction times from several hours to several minutes.[7] Aromatic nitriles (**2**) are also quickly prepared by one-step reaction of aldehydes (**1**) with hydroxylamine hydrochloride in *N*-methyl-2-pyrrolidinone (NMP) by microwave heating.[8] Many kinds of aldehydes (**1**) are commercially available and cheaper than nitriles (**2**). Hence, if the two microwave-assisted reactions can be successively combined in a vessel without any separation, more practically useful preparation of **4** from **1** should be achieved.



In order to optimize the two step reactions, we first examined which kind of solvent should be used for the transformation of aldehydes (**1**) to nitriles (**2**). A mixture of 4-bromobenzaldehyde (**1f**, 10 mmol) and hydroxylamine (10 mmol) hydrochloride was submitted to microwave irradiation in several high polar and high boiling point solvent and ionic solvent (Table 1). The every reaction temperature was measured by fiber thermometer and regulated to be kept up to around 200 ℃ by intermittent irradiation. Presence of 5 mL of NMP and 1,3-dimethyl-2-imidazolidinone gave 4-bromobenzonitrile (**2f**) in high yields by microwave irradiation for 3 min (Entries 4 and 5), but ethylene glycol and two ionic solvents in slightly lower yields

(Entries 6-8). In the absence of solvent, the reaction did not proceed even by prolonged irradiation for 45 min because the temperature was not elevated. We selected NMP as the solvent for the first step reaction from **1** to **2** due to much cheaper than 1,3-dimethyl-2-imidazolidinone. Next, effect of amount of NMP was examined; presence of 0.5 mL of NMP gave almost constant yields of 91-93% (Entries 1-4). However, 0.5 mL of NMP needed slightly longer irradiation time for 5 min to complete the reaction. Thereafter, 1 mL of NMP was adopted.

Table 1. Effect of solvents on the transformation of 4-bromobenzaldehyde (**1f**) to 4-bromobenzonitrile (**2f**)

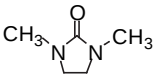
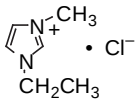
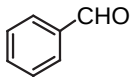
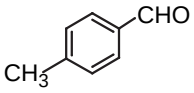
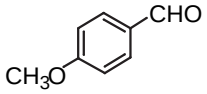
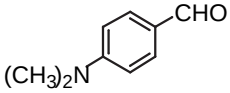
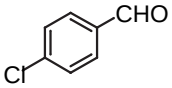
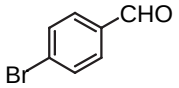
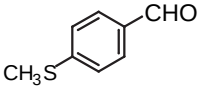
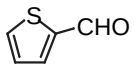
Entry	Solvent	(mL)	Irrad time (min)	Yield (%)
1		0.5	5	93
2		1	3	91
3		3	3	91
4		5	3	91
5		5	3	90
6	$HOCH_2CH_2OH$	5	10	77
7		5	2	70
8	$(n\text{-}C_4H_9)_4N^+ \bullet Br^-$	5	5	83

Table 2 summarizes the results of transformation of various aldehydes (**1**) to nitriles (**2**). Substituted benzaldehydes (**1b-g**) afforded the corresponding nitriles (**2b-g**) in high isolated yields of 82-96% by microwave irradiation for 2-5 min and then filtration of the water slurry of reaction mixtures (Entries 2-7). Benzonitrile (**2a**) and 2-thiophenecarbonitrile (**2h**) were extracted with ethyl acetate because the two nitriles are liquid at room temperature, giving moderate yields (Entries 1 and 8).

Next, we examined the conditions for the second step reaction of nitriles (**2**) to 4-amino-1,2,4-triazoles (**4**). After the first step reaction of 4-bromobenzaldehyde (**1f**), hydrazine dihydrochloride (0.75 equiv.) and hydrazine hydrate (3.0 equiv.) were directly added to the reaction mixture without any separation. However, transformation from **2f** to 3,5-bis(4-bromophenyl)-4-amino-1,2,4-triazole (**4f**) did not smoothly proceed by microwave heating because the solution was separated into two layers. Addition of ethylene glycol (3.0 mL) led to mix the two layers each other into homogeneous solution, and cause complete transformation to **4f** *via* orange-colored 3,6-bis(4-bromophenyl)-1,2-dihydro-1,2,4,5-tetrazine (**3f**) by intermittent irradiation at 160 W for 9 min at around 150 °C. Some water was added to the reaction mixture and the slurry was filtered off. Recrystallization from ethanol gave **4f** in 67% isolated yield based on initial **1f** (Table 2, Entry 6). Similarly, other aminotriazoles (**4**) were obtained from the corresponding aldehydes

(**1**) in moderate yields of 45-63% (Table 2, Entries 1-5, 7 and 8). Dihydrotetrazines (**3**) did not remained even in the crude products, easily differentiated from aminotriazoles (**4**) by ^{1}H NMR spectra. The protons bound to nitrogens in the molecule **3** appeared at a much lower field (δ, around 9 ppm) than those of **4** (δ, around 6 ppm).

Table 2. Preparation of nitriles and triazoles from aldehydes

Entry		Aldehyde **1**	Nitrile (**2**) Irrad time (min)	Nitrile (**2**) Yield (%)	Triazole (**4**) Irrad time (min)	Triazole (**4**) Yield[b] (%)
1	**a**		3	65[a]	8	45
2	**b**		3	96	10	42
3	**c**		3	82	12	55
4	**d**		2	83	12	58
5	**e**		5	84	6	46
6	**f**		3	91	9	67
7	**g**		3	85	8	62
8	**h**		3	47[a]	5	63

[a] Separated by extraction with ethyl acetate. Others were filtered off.
[b] Isolated yield based on aldehyde.

For comparison, after the first step reaction of several aldehydes (**1b**, **1c**, **1e** and **1f**), the reaction mixture was once separated by filtration, and then the second step reaction was carried out to afford **4b**, **4c**, **4e** and **4f** in 48, 59, 50 and 63% yields, respectively, showing almost comparable yields (42, 55, 46 and 67%) by successive two-step reactions without any separation (Table 2, Entries 2,3,5, and 6). Finally, conventional heating was applied to the second step reaction of the nitriles (**2b** and **2f**) separated after the first step reactions of the aldehydes (**1b** and **1f**). Long reaction times were needed for 7 and 3 hs at 130 ℃ to complete the reactions, giving the triazoles (**4b** and **4f**) in 59 and 72% yields, respectively. In conclusion, the microwave-assisted two-step synthesis of triazoles (**4**) from aldehydes (**1**) dramatically decreases the reaction times as well as effectuates the separation procedures.

EXPERIMENTAL

^{1}H-NMR spectra were measured on a JEOL JNM-GSX270 spectrometer with tetramethylsilane as an internal

standard. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Melting points were not corrected. Elemental analysis was carried out with a Yanaco CHN Corder MT-5. All the reagents were commercially available.

General procedure for preparation by microwave irradiation

A mixture of aromatic aldehyde (10 mmol) and hydroxylamine hydrochloride (0.70 g, 10 mmol) in *N*-methyl-2-pyrrolidinone (NMP, 1.0 mL, 10 mmol) was introduced into a glass test tube and placed in a domestic microwave oven (2.45 GHz) with a reflux condenser, and irradiated intermittently for 2–5 min (200 W) up to around 200 ℃. Without filtration, hydrazine dihydrochloride (0.79 g, 7.5 mmol), hydrazine monohydrate (1.50 g, 30 mmol), and ethylene glycol (3.0 mL) were added to the reaction mixture, and the whole was irradiated intermittently for 5-12 min (160 W) at around 160 ℃. After cooling, the reaction mixture was diluted with water (10 mL) and filtered off. The residue was dried and then recrystallized from ethanol.

3,5-Bis(4-methylthiophenyl)-4-amino-1,2,4-triazole (4j)

mp 219.8-221.4°C (from EtOH); ^{1}H-NMR (DMSO-d_6) δ 7.98 (d, 4H, J = 8.4 Hz), 7.41 (d, 4H, J = 8.4 Hz), 6.26 (s, 2H), 2.54 (s, 6H); IR (KBr) 3352, 3281, 3243 cm^{-1}. Anal. Calcd for $C_{10}H_8N_4S_2$: C, 58.54; H, 4.88; N, 17.07. Found: C, 58.46; H, 5.06; N, 17.08.

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