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Microwave Assisted *Mannich* Reaction of Terminal Alkynes on Alumina

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Summary. Terminal alkynes, secondary amines, and formaldehyde undergo a *Mannich* reaction at room temperature in the presence of CuCl on Al_2O_3 without any organic solvent as reaction medium. The reaction can be promoted by microwave irradiation and is complete within one minute.

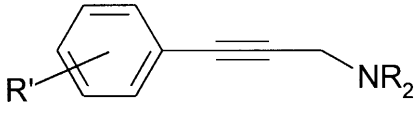
Keywords. Alkynes; Alumina; *Mannich* bases; Microwave irradiation.

Introduction

The *Mannich* reaction is one of the most important multicomponent reactions in organic chemistry [1]. *Mannich* bases are of considerable interest and have found applications in chemical and pharmaceutical industry [1g, 2].

A large variety of compounds such as ketones, nitro compounds [1b], amines [3], amides [4], and electron-rich aromatic compounds [1c, 5] can serve as substrates in *Mannich* reactions. Terminal alkynes also can take part in *Mannich* reactions to give the corresponding propargylamines which can be further transformed to β-aminoketones [6], aminoalkenes [6b, 7], or aminoalkanes [6b].

Some propargylamines exhibit biological activities. For example, substituted 1-aryl-3-aminopropynes have antiulceration, sedative, hypnotic, antispasmodic, analgesic, and anti-inflammatory effects [8]. Also, a number of 3-phenylpropyn-2-amines (**1**) have been previously prepared and shown some monoamine oxidase inhibitory, anorexigenic, and blood lipid lowering activity as well as tryptamine-like behavioural effects without any interaction with tryptamine receptors [9].



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There are several methods for the preparation of propargylamines, *e.g.* reaction of 1-(α-aminoalkyl)-benzotriazoles with lithium alkenydes [10] or with sodium

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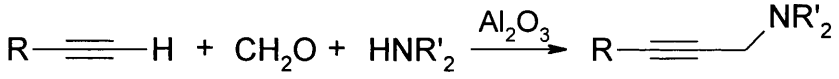
dialkynyldiethylaluminates [11], reaction of propargyl bromides with secondary amines [12], or reaction of geminal aminoethers with terminal acetylenes [13]. However, the most convenient method for the preparation of **1** is refluxing a solution of a terminal acetylene, a suitable amine, and formaldehyde in a polar solvent, mostly dioxane, in the presence of a catalytic amount of a copper salt (usually CuCl or $Cu(OAc)_2$) [6–8, 14]. Copper salts are frequently used in the reaction, since they have been found to increase the nucleophilicity of the acetylenic substrates towards the *Mannich* reactants [15]. Recently, *Dax et al*. have shown that any member of the three components can be immobilized on a resin and subsequently reacted with the other two in the presence of a copper(I) salt to afford the desired *Mannich* adducts [16].

Here, we report an environmentally benign preparation of propargylamines *via* a *Mannich* reaction on Al_2O_3 without any organic solvent as reaction medium (Scheme 1).



2 **3** **4**

Scheme 1

Results and Discussion

We have previously shown that electron-rich aromatic compounds can be aminoalkylated by a *Mannich* reaction with appropriate adducts on solid supports assisted by microwave irradiation [5b]. In continuation of our interest in *Mannich* base synthesis, in peculiar with those assisted by microwave irradiation, we examined the extension of this method to the aminomethylation of terminal alkynes with two different methods.

In method A, a terminal acetylene (**2**), a secondary amine (**3**), formaldehyde (used as 37% aqueous solution), CuCl, and neutral alumina were mixed together and stirred at room temperature. The progress of the reaction was monitored with TLC. After 6 h, the products were obtained in good to excellent yields (Table 1). This method can also be applied to bulky secondary amines, such as dibenzylamine and diisopropylamine (Table 1, entries 6 and 7). In the absence of CuCl, the yield of the reaction is negligible.

Method B is basically similar to method A, but the reaction was promoted by microwave irradiation in a domestic microwave oven. The reaction was complete in about one minute. The yields of the products were in the range of 70–94%, *i.e*. comparable to those obtained from method A (Table 1). The products **4a–i** are known compounds; the new products **4j–m** were characterized by their NMR spectra and HRMS.

To investigate solid supports other than neutral alumina, we also examined basic and acidic alumina, silica gel, and montmorillonite K-10, but the best results were obtained with neutral alumina.

Table 1. Aminomethylation of terminal alkynes on alumina at room temperature (A) or assisted by microwave irradiation (B)

Entry	Alkyne **2** (*R*)	Amine **3** (HNR'_2)	Product	Yield/%	
				A	B
1	Ph	$HNEt_2$	**4a**	83	87
2	Ph	$HNBu_2$	**4b**	86	81
3	Ph	pyrrolidine	**4c**	92	94
4	Ph	piperidine	**4d**	95	92
5	Ph	morpholine	**4e**	86	91
6	Ph	$HN(CH_2Ph)_2$	**4f**	86	88
7	Ph	$HN(i\text{-}Pr)_2$	**4g**	73	70
8	Ph	HNMePh	**4h**	83	80
9	$PhMeNCH_2$	Piperidine	**4i**	88	90
10	1-Naphthyl-OCH_2	$HNEt_2$	**4j**	77	85
11	1-Naphthyl-OCH_2	pyrrolidine	**4k**	80	91
12	1-Naphthyl-OCH_2	piperidine	**4l**	85	87
13	1-Naphthyl-OCH_2	morpholine	**4m**	84	90

In conclusion, we report herein a new method for the preparation of propargylamines using Al_2O_3, in a solvent-free and environmentally friendly reaction. The reaction time is dramatically reduced from several hours to one minute using microwave irradiation. Extending this method to the preparation of other classes of *Mannich* bases is under investigation.

Experimental

^1H NMR (80 MHz or 300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker 80 MHz or Bruker WP 300 MHz spectrometer in $CDCl_3$ using *TMS* as internal standard. HRMS were obtained on a Finnigan MAT system MAT 212. Microwave induced reactions were carried out in a domestic microwave oven Moulinex Micro-Chef (900 W) at 2450 MHz. The aluminum oxide employed was Fluka type 507 C neutral, *pH* 7.0 ± 0.5, particle size 0.05–0.15 mm.

General procedure for the preparation of propargylamines on neutral alumina at room temperature (method A)

A mixture of 2 mmol terminal acetylene, 2.1 mmol secondary amine, 2 mmol formaldehyde (used as 37% aqueous solution), 0.2 mmol CuCl, and 3 g neutral alumina was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC. Then, the mixture was extracted with ethyl acetate ($3 \times 20\,cm^3$) and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified by chromatography over a short column of silica gel (eluent : petroleum ether : ethyl acetate = 5 : 1).

General procedure for the preparation of propargylamines on neutral alumina under microwave irradiation (method B)

2 mmol terminal acetylene, 2.1 mmol secondary amine, 2 mmol formaldehyde (used as 37% aqueous solution), 0.2 mmol CuCl, and 3 g neutral alumina were mixed together, put in a 25 cm^3 beaker, and

irradiated in a microwave oven three times (each time for 20 s 3 min intervals). After cooling, the mixture was extracted with ethyl acetate ($3 \times 20\,cm^3$) and filtered. Evaporation of the solvent under reduced pressure afforded the crude product which was purified as given above.

Diethyl-(3-phenyl-prop-2-ynyl)-amine (**4a**) [11]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 1.0 (t, $2CH_3$), 2.4 (q, $2CH_2$), 3.5 (s, CH_2), 7.1–7.4 (m, $5H_{arom}$) ppm.

Dibutyl-(3-phenyl-prop-2-ynyl)-amine (**4b**) [17]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 0.9–1.1 (m, 14H), 2.1–2.4 (t, $2CH_2$), 3.5 (s, CH_2), 7.1–7.4 (m, $5H_{arom}$) ppm.

1-(3-Phenyl-prop-2-ynyl)-pyrrolidine (**4c**) [10]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 1.5–1.7 (m, $2CH_2$), 2.5–2.7 (m, $2CH_2$), 3.5 (s, CH_2), 7.1–7.4 (m, $5H_{arom}$) ppm.

1-(3-Phenyl-prop-2-ynyl)-piperidine (**4d**) [14a]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 1.1–1.7 (m, $3CH_2$), 2.2 (t, $2CH_2$), 3.5 (s, CH_2), 7.1–7.5 (m, $5H_{arom}$) ppm.

4-(3-Phenyl-prop-2-ynyl)-morpholine (**4e**) [14a]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 2.4–2.6 (t, $2CH_2$), 3.0–3.6 (t, $2CH_2$), 3.5 (s, CH_2), 7.1–7.5 (m, $5H_{arom}$) ppm.

Dibenzyl-(3-phenyl-prop-2-ynyl)-amine (**4f**) [10]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 3.4 (s, CH_2), 3.7 (s, $2CH_2$), 7.2–7.4 (m, $15H_{arom}$) ppm.

Diisopropyl-(3-phenyl-prop-2-ynyl)-amine (**4g**) [9]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 1.1 (d, $4CH_3$), 3.3 (hept, 2CH), 3.7 (s, CH_2), 7.1–7.3 (m, $5H_{arom}$) ppm.

*Methyl-phenyl-(3-phenyl-prop-2-ynyl)-amine (***4h**) [11]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 3.1 (s, CH_3), 4.4 (s, CH_2), 7.0–7.4 (m, $10H_{arom}$) ppm.

Methyl-phenyl-(4-piperidin-1-yl-but-2-ynyl)-amine (**4i**) [14c]

^{1}H NMR ($CDCl_3$, δ, 80 MHz): 1.4–1.5 (m, $3CH_2$), 2.2–2.3 (t, $2CH_2$), 2.9 (s, CH_3), 3.1 (t, CH_2), 4.0 (t, CH_2), 6.6–7.3 (m, $5H_{arom}$) ppm.

Diethyl-(4-(naphthalen-2-yloxy)-but-2-ynyl)-amine (**4j**; $C_{18}H_{21}NO$)

^{1}H NMR ($CDCl_3$, δ, 300 MHz): 0.95–1.05 (t, $2CH_3$), 2.40–2.50 (q, $2CH_2$), 3.42 (s, CH_2), 4.84 (s, CH_2), 6.84–6.95 (d, $1H_{arom}$), 7.25–7.35 (t, $1H_{arom}$), 7.36–7.49 (m, $3H_{arom}$), 7.69–7.79 (m, $1H_{arom}$),

8.21–8.31 (m, $1H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 12.3, 40.8, 47.0, 56.4, 79.5, 82.4, 105.6, 120.7, 121.9, 125.0, 125.4, 125.7, 126.2, 127.2, 134.4, 153.3 ppm; HRMS (EI): calcd. 267.1623, found 267.1624.

1-(4-(Naphthalen-2-yloxy)-but-2-ynyl)-pyrrolidine (**4k**; $C_{18}H_{19}NO$)

^1H NMR ($CDCl_3$, δ, 300 MHz): 1.70–1.78 (m, $2CH_2$), 2.51–2.60 (m, $2CH_2$), 3.43 (s, CH_2), 4.90 (s, CH_2), 6.89–6.96 (d, $1H_{arom}$), 7.29–7.39 (t, $1H_{arom}$), 7.39–7.51 (m, $3H_{arom}$), 7.70–7.83 (m, $1H_{arom}$), 8.20–8.32 (m, $1H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 23.7, 43.2, 52.4, 56.5, 79.0, 83.5, 105.7, 120.8, 122.0, 125.2, 125.5, 125.7, 126.3, 127.3, 134.4, 153.4 ppm; HRMS (EI): calcd. 265.1467, found 265.1465.

1-(4-(Naphthalen-2-yloxy)-but-2-ynyl)-piperidine (**4l**; $C_{19}H_{21}NO$)

^1H NMR ($CDCl_3$, δ, 300 MHz): 1.27–1.39 (m, CH_2), 1.48–1.63 (m, $2CH_2$), 2.32–2.45 (t, $2CH_2$), 3.25 (s, CH_2), 4.85 (s, CH_2), 6.85–6.95 (d, $1H_{arom}$), 7.26–7.35 (t, $1H_{arom}$), 7.36–7.48 (m, $3H_{arom}$), 7.68–7.79 (m, $1H_{arom}$), 8.21–8.31 (m, $1H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 23.5, 25.6, 47.6, 53.0, 56.3, 79.4, 83.0, 105.5, 120.6, 121.8, 124.9, 125.2, 125.5, 125.7, 126.0, 127.1, 134.2, 153.2 ppm; HRMS (CI, isobutane): calcd. 280.1701, found 280.1697.

4-(4-(Naphthalen-2-yloxy)-but-2-ynyl)-morpholine (**4m**; $C_{18}H_{19}NO_2$)

^1H NMR ($CDCl_3$, δ, 300 MHz): 2.37–2.46 (t, $2CH_2$), 3.22 (s, CH_2), 3.57–3.70 (t, $2CH_2$), 4.84 (s, CH_2), 6.80–6.90 (d, $1H_{arom}$), 7.25–7.35 (t, $1H_{arom}$), 7.35–7.50 (m, $3H_{arom}$), 7.70–7.80 (m, $1H_{arom}$), 8.20–8.30 (m, $1H_{arom}$) ppm; ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 47.0, 51.9, 56.1, 66.4, 79.9, 82.2, 105.4, 120.6, 121.7, 124.9, 125.2, 125.4, 125.8, 126.1, 127.1, 134.2, 153.1 ppm; HRMS (EI): calcd. 281.1416, found 281.1416.

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