Note

Microwave-enhanced Mannich Condensation of Terminal Alkynes, Primary Amines with Paraformaldehyde on Cuprous Iodide Doped Alumina under Solvent Free Conditions

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A microwave-enhanced, solventless Mannich condensation of terminal alkynes, primary amines with paraformaldehyde on cuprous iodide doped alumina has been investigated. The structures of products depend on the ratio of alkyne to amine and paraformaldehyde.

Keywords Mannich condensation, terminal alkyne, paraformaldehyde, primary amine, cuprous iodide, alumina, solvent free, microwave irradiation

Introduction

The Mannich reaction is a classic example of three-components condensation reaction.[1-5] Generally, formaldehyde or paraformaldehyde, an amine and an "active-hydrogen" component such as an enolizable ketone or terminal alkyne is allowed to react to afford the corresponding β-aminoketone or β-aminoalkyne. The latter Mannich adduct contains at least two potential sites for further modification, *i.e.*, the amine and the alkyne.[6,7] In addition, β-aminoalkyne and its derivatives have a wide range of application including use as pharmaceutical intermediates[8] and as general synthetic building blocks.[9-12] Moreover, the alkyne moiety presents an opportunity for synthetic elaboration. The traditional Mannich reaction for the synthesis of β-aminoalkyne often requires drastic reaction conditions and generally utilize dioxane and DMF, the toxic solvents. The organic solvents and the metal catalyst were difficult to handle and a number of waste handling problems were existed.

We have found that a microwave-enhanced Mannich condensation of terminal alkynes with secondary amines and paraformaldehyde on CuI-doped alumina in the absence of solvents afforded the corresponding aminomethylated adducts in good yields. The reaction can be extended to the Mannich condensation followed by cyclization reaction of *o*-ethynylphenol, seconadery amines with paraformaldehyde leading to 2-(dialkylamniomethyl) benzo[b]furans in a one-pot manner.[13,14]

In order to investigate this reaction extensively, we wish to report a novel microwave-enhanced Mannich condensation of terminal alkynes with primary amines and paraformaldehyde on CuI-doped alumina in the absence of solvents. The structures of products depend on the ratio of alkyne to amine and paraformaldehyde. A *bis*-Mannich condensation product **4** was formed when the ratio of primary amine to terminal alkyne and paraformaldehyde is 1:2:4, a Glaser coupling product **5** was observed when the ratio of primary amine to terminal alkyne and paraformaldehyde is 3:1:1.3, and *N*-methyl-β-aminoalkyne **6** was produced through a Mannich condensation followed by reductive methylation sequence reaction procedure when the ratio is 1:1:3.

Results and discussion

Effect of cuprous salts on the Mannich condensation of terminal alkynes with primary amines and paraformaldehyde

Our initial studies were directed towards exploring the effect of cuprous salts on the Mannich condensation of terminal alkynes with amines and paraformaldehyde. The results are listed in Table 1. Benzylamine and 1-decyne were chosen as the model Mannich reactants for this investigation.

It is obvious that the Mannich condensation reaction requires a cuprous salt to "activate" the terminal proton of

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Table 1 Effect of cuprous salts on the Mannich condensation[a]

Entry	Cuprous salt	Yield[b](%)
a	CuCl	23
b	CuBr	21
c	CuI	71
d	—	0

[a] Reaction scale: benzylamine (1.00 mmol), 1-decyne (2.00 mmol), paraformaldehyde (4.00 mmol), cuprous salt (2.00 mmol), alumina (1.00 g), 900 W microwave oven (Glanze WD900SL23 2 at 2450 MHz) used at 100 % power for 2 min. [b] Isolated yields.

an alkyne to promote the reaction. Among the cuprous salts we tested, cuprous iodide is most effective and was chosen for the further study.

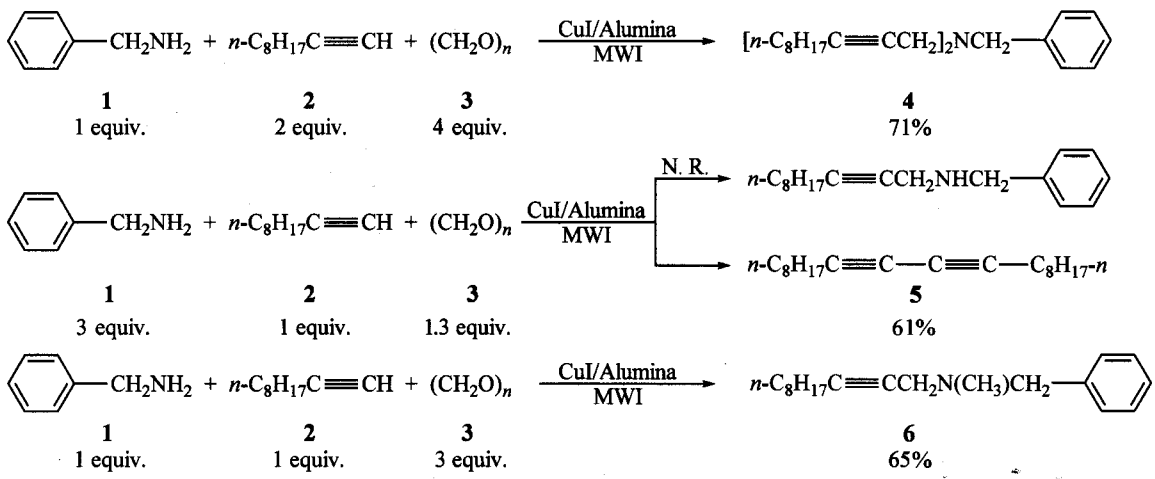
Mannich condensation of terminal alkynes with primary amine and paraformaldehyde

As anticipated, benzylamine (1 equiv.), a primary amine, reacted with 1-decyne (2 equiv.) and paraformaldehyde (4 equiv.) to produce the *bis*-Mannich condensation product **4** because of two nitrogen-hydrogen bonds in primary amine (Scheme 1). However, the reaction of benzylamine (3 equiv.) with 1-decyne (1 equiv.) and paraformaldehyde (1.3 equiv.) could not afford a secondary amine product via a single Mannich condensation step (Scheme 1), but a Glaser coupling product **5** was observed (Scheme 1). Interestingly, when the ratio of benzylamine to 1-decyne and paraformaldehyde is 1∶1∶3, a Mannich condensation followed by reductive methylation product **6** was obtained (Scheme 1).

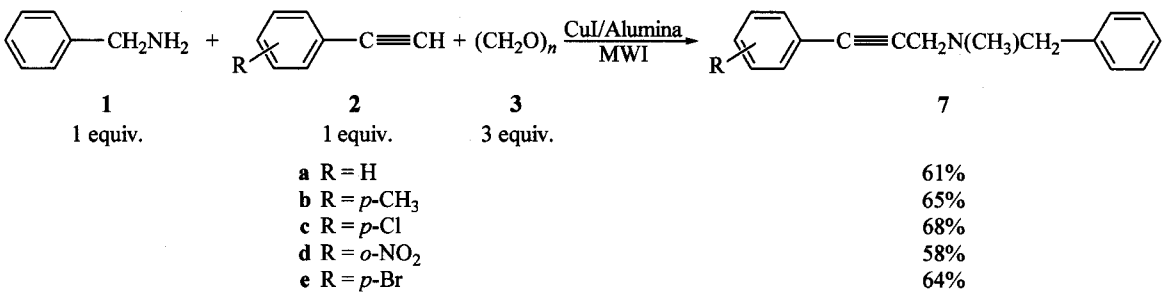
Terminal aromatic alkynes, such as phenylacetylene, *p*-ethynyltoluene, *p*-chlorophenylacetylene, *o*-nitrophenylacetylene or *p*-bromophenylacetylene (1 equiv.) was successful to react with benzylamine (1 equiv.) and paraformaldehyde (3 equiv.) to afford the Mannich condensation followed by reductive methylation sequence reaction products in good yields (Scheme 2). It provides an alternative route to *N*-methyl-*β*-aminoalkyne through a Mannich condensation of terminal alkyne with primary amine and paraformaldehyde in one-pot under solvent free reaction conditions. Compared to the general reductive methylation methods,[15-17] this way is more simple, convenient, effective and environmentally friendly.

Although the detailed reaction mechanism is not clear, the reaction presumably proceeds through the Cu (I)-assisted condensation of terminal alkynes with primary amines and paraformaldehyde to form a *bis*-Mannich condensation product or a Mannich condensation followed by reductive methylation product (depend on the ratio of reactants). Meanwhile, a Glaser coupling product of terminal alkyne was generated via an oxidation of terminal alkyne followed by self-coupling sequence reaction procedure. Further investigation is currently underway.

Scheme 1



Scheme 2



Surface recyclability

We utilized a surface containing 1 mmol of cuprous iodide per gram of alumina for a 1 mmol scale reaction. In an effort to enhance the efficiency of the new solid-state Mannich condensation and reduce the inorganic waste (CuI/Al_2O_3), recycling of cuprous iodide doped alumina was investigated. Table 2 contains a summary of the results. It can be seen that the catalyst and alumina remains active at least after eight cycles. After the product was removed from the solid surface using an organic solvent, CuI/Al_2O_3 can be used for the next trial directly without any treatment.

Table 2 Successive trials for Mannich condensation using CuI/Al_2O_3[a]

Trial	Yield[b](%)	Trial	Yield[b](%)
1	71	5	68
2	68	6	69
3	67	7	67
4	70	8	66

[a] Experiment was carried out as described in the experimental procedure by using 1-decyne (1.00 mmol), benzylamine (1.00 mmol), paraformaldehyde (3.00 mmol), cuprous salt (1.00 mmol), alumina (1.00 g), 900 W microwave oven (Glanze WD900SL23-2 at 2450 MHz) used at 100% power for 2 min. [b] Isolated yields.

Conclusion

A reliable, rapid, practical and environmentally benign method for the synthesizing *N*-methyl-*β*-aminoalkynes has been developed using the solvent-free Mannich condensation of terminal alkynes with primary amines and paraformaldehyde in one-pot. The process is highly efficient, and does not require pre-forming the iminium species and is not hampered by the heterogeneity of the reaction.

Experimental

All ^1H NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AZ 300 spectrometer. Chemical shift are given as δ value with reference to tetramethylsilane (TMS) as internal standard. GC/MS data were obtained by using a Hewlett-Packard 6890 series GC equipped with a 5983 mass selective detector. A commercial available Glanze WD900SL23-2, 900 W microwave oven was utilized at 2450 MHz. Alumina (activated, neutral, Brockmann I, *ca*. 150 mesh) and cuprous iodide were purchased from Aldrich Chemical Co. without any treatment prior to use. Silica gel was received from Qingdao Ocean Chemical Factory (China). Other reagents were of analytical grade and from commercial supplier. Products were purified by flash chromatography.

General procedure of the Mannich condensation reaction of terminal alkyne with primary amine and paraformaldehyde

(a) 1-Decyne (2.00 mmol), paraformaldehyde (4.00 mmol) and benzylamine (1.00 mmol) were mixed with cuprous iodide (0.38 g, 2.00 mmol) doped alumina (1.00 g) in a 10 mL clean dry round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 100% power for 2 min. After cooling, ethyl ether (4 mL) was added and the slurry was stirred at room temperature to ensure the complete removal of the product from alumina. The mixture was under vacuum filtered using a sintered glass funnel and separated by flash chromatography to yield the *bis*-Mannich condensation adduct.

(b) 1-Decyne (1.00 mmol), paraformaldehyde (1.30 mmol) and benzylamine (3.00 mmol) were mixed with cuprous iodide (0.19 g, 1.00 mmol) doped alumina (1.00 g) and placed in the microwave oven and irradiated at 100 % power for 2 min. After the usual workup described above, the mixture was separated by flash chromatography to give the Glaser coupling product.

(c) Terminal alkyne (1.00 mmol), paraformaldehyde (3.00 mmol) and benzylamine (1.00 mmol) mixed with cuprous iodide (0.19 g, 1.00 mmol) doped alumina (1.00 g) and placed in the microwave oven and irradiated at 100% power for 2 min. After usual workup described above, the mixture was separated by flash chromatography to give the Mannich condensation followed by reductive methylation product.

General procedure for recycling

After carried out a Mannich condensation, ethyl ether was added to remove the product from cuprous iodide doped alumina surface. After filtration, CuI/Al_2O_3 was directly used for the next trial.

Benzyldi(undec-2-ynyl)amine (**4**) Oil; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.38—7.20 (m, 5H), 3.66 (s, 2H), 3.35 (s, 2×2H), 2.21 (t, J = 6.7 Hz, 2×2H), 1.55—1.28 (m, 2×12H), 0.88 (t, J = 6.6 Hz, 2×3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.3, 129.3, 128.1, 127.1, 85.3, 75.0, 56.9, 42.3, 31.8, 29.2, 29.1, 28.9, 22.6, 18.7, 14.0; IR (film) ν: 2232 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 322 (M^+ − 85, 6), 294 (7), 184 (5), 156 (8), 91 (100). Anal. calcd for $C_{29}H_{45}N$: C 85.44, H 11.13, N 3.44; found C 85.37, H 11.24, N 3.52.

9,11-*Eicosdiyne* (**5**) Oil;[18] ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.23 (t, J = 6.8 Hz, 2×2H), 1.57—1.27 (m, 2×12H), 0.88 (t, J = 6.3 Hz, 2×3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 77.5, 65.3, 31.8, 29.1, 29.0, 28.8, 28.4, 22.6, 19.1, 14.0; IR (film) ν: 2147 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 254 (M^+ − C_2H_5, 2), 217 (5), 175 (8), 161 (16), 147 (24),

133 (29), 119 (42), 105 (56), 91 (100).

Benzylmethyl(undec-2-ynyl)amine (**6**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35—7.22 (m, 5H), 3.55 (s, 2H), 3.26 (t, J = 2.0 Hz, 2H), 2.30 (s, 3H), 2.26—2.20 (m, 2H), 1.59—1.28 (m, 12H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.6, 129.2, 128.2, 127.1, 85.8, 74.6, 60.2, 45.5, 41.8, 31.8, 29.2, 29.1, 29.0, 28.9, 22.6, 18.7, 14.0; IR (film) ν: 2260 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 271 (M^+, 7), 194 (25), 158 (22), 120 (18), 91 (100). Anal. calcd for $C_{19}H_{29}N$: C 84.07, H 10.77, N 5.16; found C 83.96, H 10.85, N 5.19.

Benzylmethyl(3-phenyl-prop-2-ynyl)amine (**7a**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.48—7.44 (m, 2H), 7.38—7.23 (m, 8H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.3, 131.6, 129.1, 128.1, 127.9, 127.1, 123.2, 85.6, 84.3, 60.1, 45.6, 41.8; IR (film) ν: 2235 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 235 (M^+, 18), 158 (41), 144 (27), 115 (100), 91 (64). Anal. calcd for $C_{17}H_{17}N$: C 86.77, H 7.28, N 5.95; found C 86.66, H 7.43, N 6.01.

Benzylmethyl(3-p-tolyl-prop-2-ynyl)amine (**7b**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.37—7.24 (m, 7H), 7.09 (d, J = 7.94 Hz, 2H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.4, 137.9, 131.5, 129.1, 128.9, 128.2, 127.1, 120.2, 85.7, 83.6, 60.2, 45.7, 41.9, 21.3; IR (film) ν: 2247 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 249 (M^+, 17), 172 (32), 158 (36), 129 (100), 91 (73). Anal. calcd for $C_{18}H_{19}N$: C 86.70, H 7.68, N 5.62; found C 86.42, H 7.60, N 5.57.

Benzylmethyl [3-(4-*chlorophenyl*)-*prop*-2-*ynyl*] *amine* (**7c**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.38—7.24 (m, 9H), 3.61 (s, 2H), 3.48 (s, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.2, 133.9, 132.8, 129.1, 128.5, 128.2, 127.1, 121.6, 85.5, 84.4, 60.2, 45.6, 41.9; IR (film) ν: 2251 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 271, 269 (M^+, 6, 17), 192 (30), 178 (32), 158 (14), 149 (91), 132 (15), 114 (17), 91 (100). Anal. calcd for $C_{17}H_{16}NCl$: C 75.69, H 5.98, N 5.19; found C 75.53, H 6.06, N 5.33.

Benzylmethyl[3-(2-*nitrophenyl*)-*prop*-2-*ynyl*]*amine* (**7d**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.01 (dd, J = 8.21, 1.08 Hz, 1H), 7.64—7.51 (m, 2H), 7.45—7.26 (m, 6H), 3.69 (s, 2H), 3.58 (s, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 149.7, 138.2, 134.8, 132.6, 129.1, 128.3, 128.2, 127.1, 124.4, 118.4, 93.3, 80.9, 59.9, 45.6, 41.9; IR (film) ν: 2268 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 280 (M^+, 4), 263 (14), 203 (10), 189 (6), 144 (18), 132 (20), 120 (19), 104 (16), 91 (100). Anal. calcd for $C_{17}H_{16}N_2O_2$: C 72.84, H 5.75, N 9.99; found C 72.63, H 5.82, N 9.91.

Benzylmethyl [3-(4-*bromophenyl*)-*prop*-2-*ynyl*] *amine* (**7e**) Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (d, J = 7.76 Hz, 2H), 7.28 (d, J = 7.96 Hz, 2H), 7.18—7.04 (m, 5H), 3.62 (s, 2H), 3.15 (s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 138.3, 135.8, 132.4, 129.1, 128.4, 128.1, 127.0, 121.4, 85.8, 84.6, 60.5, 45.7, 41.9; IR (film) ν: 2257 (C≡C) cm^{-1}; MS (70 eV) m/z (%): 315, 317 (M^+, 8, 9), 238 (23), 224 (27), 204 (11), 160 (67), 132 (15), 115(17), 91 (100). Anal. calcd for $C_{17}H_{16}NBr$: C 64.98, H 5.13, N 4.46; found C 65.12, H 5.01, N 4.59.

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