A facile solvent-free one-pot three-component Mannich reaction of aldehydes, amines and terminal alkynes catalysed by $CuCl_2$

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A solventless Mannich condensation of aldehydes, amines, and terminal alkynes catalysed by 10 mol% of $CuCl_2$ was investigated. The components were simply mixed and heated together under vacuum, without any need of solid-support or solvent. This results in the formation of Mannich products in high yields.

Keywords: Mannich reaction, aldehydes, alkynes, solvent-free synthesis, copper salt

Multi-component reactions are some of the most important reactions in organic synthesis. The Mannich reaction is a well-known example of a three-component reaction in which an aldehyde (usually formaldehyde), ammonia or a primary or secondary amine and a compound having an acidic C–H bonding site such as an enolisable ketone, an electron rich aromatic, a nitro compound or a terminal alkyne are condensed to afford the corresponding products which are usually called Mannich bases.[1] The products are used extensively in industry, pharmacology and organic synthesis.[2]

The classic method for the Mannich reaction suffers from some disadvantages and limitations such as low yields, restriction to non-enolisable aldehydes and drastic reaction conditions such as refluxing of the reagents in toxic solvents like dioxane, acetonitrile, toluene, *etc.*[1a] Modern variations of the Mannich reaction have been developed in past decades to overcome these drawbacks, including the use of *pre-* or *in situ* prepared imminium salts,[1,3] microwave-assisted methods on solid supports[4] and more recently, performing the reaction in aqueous solution.[5] The latter meets the increasing interest nowadays in developing environmentally-benign methods removing the need for organic solvents as reaction media.

The one-pot variations among others, profit from the ease of the methodology, simple laboratory equipment and the possibility of using non-modified reagents.[3]

Solid–solid, solid–melt and melt reactions have recently been developed as eco-friendly procedures which afford high yields and do not require any auxiliaries such as solid-supports, organic solvents, or microwave acceleration. These methods have been successfully used in different type of reactions including protection, condensation and elimination.[6] For example, it has been reported that the Knoevenagel reaction is viable if the reagents are mixed and heated in an evacuated vessel.[7] In this respect and towards our goal of developing new solventless methods of preparation of organic compounds, we were interested in developing a new method for the Mannich reaction which combines the advantages of solvent-free methods, one-pot procedures, and avoids the need for solid-supports.

We now wish to report a one-pot, three-component Mannich reaction catalysed by $CuCl_2$, simply by heating a mixture of the reagents in an ordinary laboratory oven. No reaction solvent, no solid support or acceleration by microwave irradiation is needed.

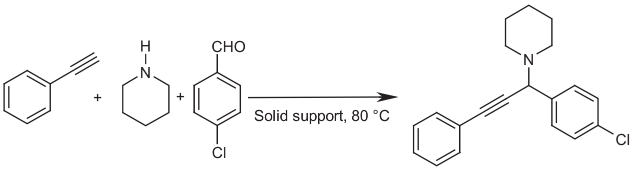
Very recently, there has been a report on a microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina which gave the corresponding Mannich products in good yields.[4b] Despite of the usefulness of the method, it is restricted to using of *para*-formaldehyde and the rôle of alumina (1 g per 1 mmol of aldehyde) has not been clearly investigated. As it has been proved in recent years that using some auxiliaries in such reactions is *NOT* necessary,[7] we were interested to explore the necessity and efficiency of solid supports, and to study the scope of the method for other aldehydes than formaldehyde (including enolisable ones). We have investigated, therefore, the reaction of phenylacetylene, piperidine and *p*-chlorobenzaldehyde as a model reaction in the presence of SiO_2, alumina (acidic and basic) or Montmorillonite K-10 (Scheme 1).

To a mixture of *p*-chlorobenzaldehyde (1.0 mmol), phenylacetylene (1.2 mmol) and piperidine (1.2 mmol) in a 10 ml flask, 1.0 g. of the corresponding solid-support was added (Table 1). The flask was evacuated and heated to 80°C for the given time. The results are summarised in Table 1.

Interestingly, the best result was obtained when using only 10 mol% of $CuCl_2$ catalyst (instead of 3 equivalents as used in other methods[4b]) and no solid support at all. It seemed that the presence of a solid support was not strictly necessary.

A wide range of potential catalysts such as $FeCl_3$, $ZnCl_2$, $CeCl_3.7H_2O$, $CoCl_2.6H_2O$, $BiCl_3$, CuI and $CuCl_2$ were tested in the model reaction. The last was the most effective one and was chosen for further investigations (Table 2).

These results have encouraged us to investigate the usefulness of this methodology for other substrates. Table 3 contains a summary of the results. All of the known products **4a**–**4p** were been characterised with comparison of their physical or spectral data with those in the literature. The new products **4q**–**4s** exhibit satisfactory elemental analysis and spectroscopic data.



Scheme 1 Solvent-free reaction of phenyl-acetylene, piperidine and *p*-chlorobenzaldehyde.

Table 1 Effect of different solid-supports on sample Mannich condensation reaction

Solid-support	Time/h	Yield/%
SiO_2	3	9
SiO_2	20	30
Al_2O_3 (basic)	3	34
Al_2O_3 (basic)	20	60
Al_2O_3 (acidic)	3	16
Al_2O_3 (acidic)	20	72
Montmorillonite K10	3	15
Montmorillonite K10	20	85
10 mol% $CuCl_2$	3	95

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Table 2 Effect of different catalysts on sample Mannich condensation reaction (Scheme 1)[a]

Entry	Catalyst	Yield/%
1	$FeCl_3$	14
2	$ZnCl_2$	37
3	$CeCl_3.7H_2O$	3
4	$CoCl_2.6H_2O$	7
5	$BiCl_3$	8
6	CuI	87
7	$CuCl_2$	95

[a] After 3 h at 80°C with 10 mol% catalyst.

The method is very efficient, as a wide range of different aldehydes (not only formaldehyde), and amines with phenylacetylene (**2a**), 1-octyne (**2b**), and or 1-heptyne (**2c**) were successfully condensed to afford the corresponding Mannich products. This solventless approach provides ready access to propargylamines and is applicable both to non-enolisable aldehydes such as benzaldehyde and its derivatives (entries 1–4, 11–19), and formaldehyde (entries 7–10), as well as enolisable aldehydes, such as *n*-hexanal and *n*-octanal (entries 5 and 6). Both primary amines like aniline and secondary amines including sterically hindered dibenzylamine afforded good yields.

In summary, we have reported here an environmentally friendly Mannich condensation of terminal alkynes, aldehydes and amines by simply mixing the reagents and only 10 mol% of $CuCl_2$ catalyst and heating at temperatures up to 80°C in an evacuated vessel affording the desired products in high yields. No reaction solvent, no solid support or acceleration by microwave irradiation was needed.

Table 3 Mannich condensation of aldehydes, alkynes and amines

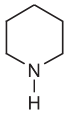
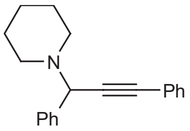
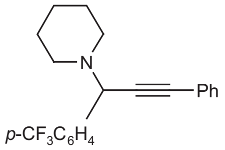
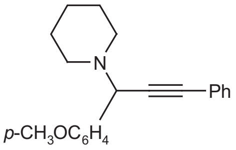
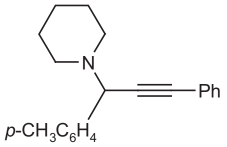
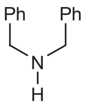
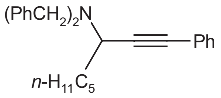
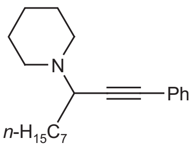
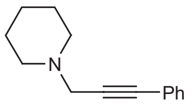
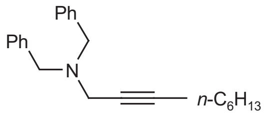
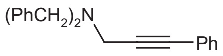
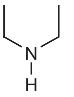
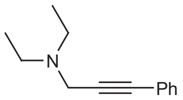
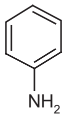
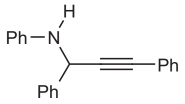
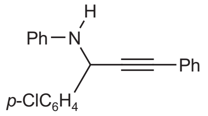
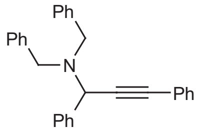
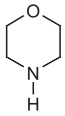
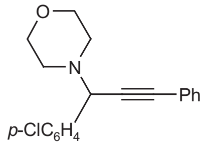
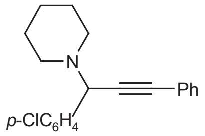
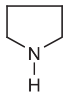
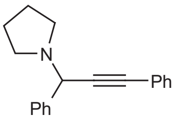
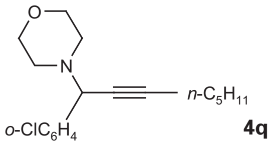
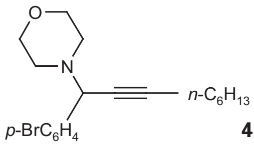
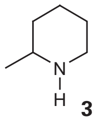
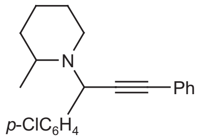
Entry	Aldehyde 1	Alkyne 2	Amine 3	Product 4[a]	Temp/°C	Yield/%
1	**1a**: C_6H_5CHO	**2a**: $C_6H_5C\equiv CH$	 **3a**	 **4a**[8]	60 80	43 85
2	**1b**: *p*-$CF_3C_6H_4CHO$	**2a**	**3a**	 **4b**[5b]	60 80	53 56
3	**1c**: *p*-$CH_3OC_6H_4CHO$	**2a**	**3a**	 **4c**[9]	80	92
4	**1d**: *p*-$CH_3C_6H_4CHO$	**2a**	**3a**	 **4d**[9]	80	88
5	**1e**: *n*-$C_5H_{11}CHO$	**2a**	 **3b**	 **4e**[4a]	80	90
6	**1f**: *n*-$C_7H_{15}CHO$	**2a**	**3a**	 **4f**[10]	80	75
7	**1g**: $(CH_2O)n$	**2a**	**3a**	 **4g**[10]	80	95
8	**1g**	**2b**: *n*-$C_6H_{13}C\equiv CH$	**3b**	 **4h**[4b]	80	92
9	**1g**	**2a**	**3a**	 **4i**[4b]	80	83

Table 3 *Continued*

Entry	Aldehyde **1**	Alkyne **2**	Amine **3**	Product **4**[a]	Temp/°C	Yield/%
10	**1g**	**2a**	 **3c**	 **4j**[11]	80	100
11	**1a**	**2a**	 **3d**	 **4k**[8]	80	80
12	**1h:** p-ClC_6H_4CHO	**2a**	**3d**	 **4l**[12]	80	93
13	**1a**	**2a**	**3b**	 **4m**[5b]	80	75
14	**1h**	**2a**	 **3e**	 **4n**[9]	80	95
15	**1h**	**2a**	**3a**	 **4o**[5b]	80	85
16	**1a**	**2a**	 **3f**	 **4p**[5c]	80	80
17	**1i:** o-ClC_6H_4CHO	**2c:** n-$C_5H_{11}C\equiv CH$	**3e**	 **4q**	80	90
18	**1j:** p-BrC_6H_4CHO	**2b**	**3e**	 **4r**	80	94
19	**1h**	**2a**	 **3g**	 **4s**	80	68

[a]The structures of the all known products were being characterised with comparison of their spectroscopic data with those reported in the cited literature.

Experimental

Melting points were determined on a hot stage or oil bath apparatus without correction. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 MHz in $CDCl_3$ using TMS as internal standard. The GC Analysis was performed with a Varian CP-3800 instrument. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. GC-MS spectra were obtained on a Fisons 8000 Trio instrument at ionisation potential of 70 ev. The structures of the all known products were being characterised with comparison of their spectroscopic data with those reported in the literature.[4,5,8-12]

General procedure for the preparation of Mannich bases from aldehydes, alkynes and amine

Aldehyde (1 mmol), alkyne (1.2 mmol), and amine (1.2 mmol) were poured in a 10 ml flask at room temperature. After addition of $CuCl_2$ (0.1 mmol) and mixing, the flask was evacuated (0.2 bar) and heated to 80°C for 3 h in a laboratory oven. The progress of reaction was monitored by GC. The reaction mixture was washed with petrol and filtered, and the solvent was evaporated on a rotary evaporator. The residue was purified with a short silica gel column (eluent:light petroleum ether/ethyl acetate, 10:1), when necessary.

4-(1-(2-chlorophenyl)oct-2-ynyl)morpholine (**4q**): A yellow oil was obtained in 90% yield; ^{1}H NMR ($CDCl_3$): δ = 0.95 (t, 3H, J = 7 Hz), 1.35–1.45 (m, 4H), 1.56–1.62 (m, 2H), 2.33 (dt, 2H, J = 2, 7.4 Hz), 2.56–2.61 (m, 4H), 3.66–3.74 (m, 4H), 4.91 (t, 1H, J = 2 Hz), 7.23–7.30 (m, 2H), 7.40 (dd, 1H, J = 1.5, 7.7 Hz), 7.71 (dd, 1H, J = 1.5, 7.7 Hz). ^{13}C NMR ($CDCl_3$): δ = 14.4, 19.1, 22.6, 29.1, 31.5, 50.1, 58.9, 67.5, 75.5, 89.1, 126.6, 129.2, 130.1, 130.9, 135.0, 136.6. MS (70 eV) *m/z* (%): 307, 305 (M^+), 262, 194, 163, 129, 86, 56. Calcd. for $C_{18}H_{24}ClNO$: C, 70.69; H, 7.91; N, 4.58; Found: C, 70.5; H, 7.9; N, 4.5.

4-(1-(4-bromophenyl)non-2-ynyl)morpholine (**4r**): A yellow oil was obtained in 94% yield; ^{1}H NMR ($CDCl_3$): δ = 0.94 (t, 3H, J = 7 Hz), 1.31–1.39 (m, 4H), 1.45–1.50 (m, 2H), 1.60 (quint, 2H, J = 7.2 Hz), 2.35 (dt, 2H, J = 2, 7.0 Hz), 2.54 (t, 4H, J = 4.5 Hz), 3.73 (m, 4H), 4.52 (t, 1H, J = 2 Hz), 7.49 (s, 4H). ^{13}C NMR ($CDCl_3$): δ = 14.5, 19.2, 23.0, 29.0, 29.3, 31.7, 50.0, 61.4, 67.5, 75.1, 89.8, 121.9, 130.7, 131.6; 138.0; MS (70 eV) *m/z* (%): 365, 363 (M^+), 334, 278, 208, 169, 86, 56. Calcd. for $C_{19}H_{26}BrNO$: C, 62.64; H, 7.19; N, 3.84; Found: C, 62.5 ,H, 7.1, N, 3.8.

1-(1-(4-chlorophenyl)-3-phenylprop-2-ynyl)-2-methylpiperidine (**4s**): A yellow oil was obtained in 68% yield; ^{1}H NMR ($CDCl_3$): δ = 1.29 (d, 3H, J = 6 Hz), 1.34–1.45 (m, 3H), 1.53–1.57 (m, 1H), 1.70–1.74 (m, 2H), 2.24–2.30 (t, 1H, J = 11.2 Hz), 2.42–2.46 (m, 1H), 2.65–2.70 (m, 1H), 5.31 (s, 1H), 7.34–7.42 (m, 5H), 7.55–7.59 (m, 2H), 7.64–7.67 (m, 2H). ^{13}C NMR ($CDCl_3$): δ = 21.1, 25.4, 26.6, 35.9, 47.3, 55.6, 55.9, 84.7, 88.9, 123.6, 128.6, 128.6, 128.8, 130.2, 132.3, 133.3, 138.7; MS (70 eV) *m/z* (%): 325, 323 (M^+), 310, 308, 226, 189, 115, 83. Calcd. for $C_{21}H_{22}ClN$: C, 77.88; H, 6.85; N, 4.32; Found: C, 77.6; H, 6.8; N, 4.3.

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