Dipyridine copper chloride-catalysed one-pot synthesis of β-amino carbonyl compounds via Mannich reaction

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$CuPy_2Cl_2$-catalysed Mannich reaction of aromatic aldehyde, aromatic amine, and acetophenone proceeded smoothly in water to afford the corresponding β-amino carbonyl compounds in excellent yields.

Keywords: Mannich reaction, aldehydes, amines, ketonesa $CuPy_2Cl_2$

The Mannich-type reactions are useful C–C bond forming reactions in organic synthesis for the preparation of β-amino ketones and other β-amino carbonyl compounds.[1-8] The β–amino carbonyl compounds are used for the synthesis of amino alcohols, peptides, lactams and as precursor to optically active amino acids. In the classical intermolecular Mannich reaction, three-components, an aldehyde, amine and a ketone, react to form a β-amino carbonyl compounds in the presence of catalysts like proline,[9-11] acetic acid,[12] *p*-dodecyl benzenesulfonic acid,[13] Lewis acids,[14,15] lanthanides,[16] transition metal salt catalysis,[17] Silica-supported aluminum chloride[18] and $NbCl_5$.[19] Despite the potential utility of this reaction, traditional protocols require somewhat harsh conditions, using toxic organic solvents and long reaction times leading to competition from undesired side reactions. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Consequently, there remains the opportunity for further development of better catalyst in the synthesis of β-amino carbonyl compounds reusability.

Result and discussion

In continuation of our studies of $CuPy_2Cl_2$[20] mediated reactions we wish to report the synthesis of β-amino carbonyl compounds via Mannich reaction in aqueous media. The catalyst is stable in air and water, soluble in water and immiscible in common organic solvents, reusable, and of high thermal stability. The reaction is completed in a short time and in excellent yields. Earlier, we have employed this catalyst for various organic transformations, such as Biginelli reaction,[21] Pechmann condensation.[22] There is a need for the development of organic reactions in environmentally-friendly media, such as water as solvent.

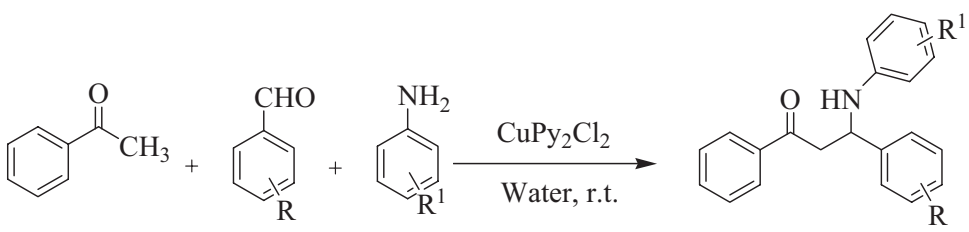
The $CuPy_2Cl_2$-catalysed Mannich reaction was examined on number of aromatic aldehydes, amines and ketones. The results are summarised in Table 1. Good yields were observed on simple aniline, 4-chloro aniline and 4-nitro aniline. 2-Nitroaniline failed to yield any product (entry 14) due to steric effects. When the reaction was carried out with piperdine (entry 15) no product was obtained.

The reaction was studied in various solvents such as water, ethanol, acetonitrile and dichloromethane. Good yields were

Table 1 $CuPy_2Cl_2$-catalysed direct Mannich reaction varios aryl aldehydes and amines

Entry	R	R^1	Time/h	Yield/%[a]	M.p./°C
1	H	H	9	95	169–170[13]
2	4-Cl	H	11	95	114–115[12]
3	4-NO_2	H	8	94	105–106[13]
4	4-CH_3	H	9	92	134–135[12]
5	4-OH	H	10	93	181–182
6	4-OCH_3	H	10	93	142–143[12]
7	H	4-Cl	12	95	170–171[12]
8	4-Cl	4-Cl	12	92	118–119[12]
9	4-CH_3	4-Cl	10	95	135–136
10	4-NO_2	4-Cl	10	93	113–114
11	4-OCH_3	4-Cl	11	91	148–149
12	4-OH	4-Cl	10	92	158–159
13	H	4-NO_2	12	95	180–181[12]
14	4-Cl	2-NO_2	56	–	–
15	H	Piperdine	48	–	–
16	4-OH	4-CH_3	8	89	171–172[12]
17	4-CH_3	4-CH_3	10	85	136–137[12]
18	4-Br	4-CH_3	8	89	126–127[12]

[a]Yields refer to isolated pure products and were characterised by NMR, IR and mass spectral data with those of authentic samples.



Scheme 1

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Table 2 $CuPy_2Cl_2$-catalysed three component Mannich reaction of benzaldehyde, amine and acetophenone in different solvents

Entry	Solvent	Yield/%
1	Water	95
2	Ethanol	95
3	Acetonitrile	89
4	DCM	65

observed in water and ethanol, moderate yields in acetonitrile and poor yields were observed in DCM. We gave more priority to water because it is environmentally-friendly solvent and also the catalyst is easily soluble and recoverable from water.

In conclusion we have shown that $CuPy_2Cl_2$ is an efficient catalyst for the Mannich reaction.

Experimental

Melting points are uncorrected. The reactions were monitored by TLC and visualised with UV light. IR spectra (KBr) were recorded on Shimidazo FTIR model 8010 spectrometer and the ^{1}H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as an internal standard. The C, H, and N analysis of the compound was done on Elementar Vario EL model. Mass spectra were recorded on a JEOL JMS D-300 Spectrometer. All solvents and reagents were purchased from Aldrich and Fluka.

Typical procedure for the synthesis of Mannich products

$CuPy_2Cl_2$ (0.01 mol%) was added to a mixture of benzaldehyde (1 equiv., 0.5 g), aniline (1 equiv., 0.45 g) and acetophenone (1 equiv., 0.6 g) in distilled water (3 ml). The mixture was stirred at room temperature. After a certain time (see Table 1), the reaction mixture became viscous and solidified. The completion of reaction was monitored by TLC. The resulting solid was filtered and recrystallised from ethanol to afford the pure compounds. The filtrate containing the catalyst could be evaporated under reduced pressure (50 mm. Hg pressure at 85ºC) to give a blue solid and it can be reused for the next reaction with only modest loss in activity.

Analytical data for the Mannich products

3-(4-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (**2**): ^{1}H NMR (200 MHz, $CDCl_3$): 3.40(2H, d, J = 6.4 Hz), 4.92(1H, t, J = 6.4 Hz), 6.49(2H, d, J = 7.9 Hz), 6.65(1H, t, J = 7.6 Hz), 7.05(1H, t, J = 7.6 Hz), 7.25(2H, d, J = 7.1 Hz), 7.35–7.75(6H, m), 7.85(1H, d, J = 7.9 Hz), 8.00 (1H, d, J = 7.8 Hz); IR(cm^{-1}): 3389, 3034, 1674, 1595, 1518, 1375,1295, 1225, 1081, 1005, 932, 860, 749, 690, 620, 515. EIMS, 70Ev, *m/z*: 335 (M^+); Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17; Found: C, 75.14; H, 5.43; N, 4.15%.

3-(4-hydroxyphenyl)-1-phenyl-3-(phenylamino)propan-1-one (**5**): ^{1}H NMR(200 MHz, $CDCl_3$): 3.40(2H, m), 4.90(1H, t, J = 6.0 Hz), 6.45(2H, d, J = 7.5 Hz), 6.65(1H, t, J = 7.1 Hz), 7.15(2H, m), 7.15(1H, d, J = 7.9 Hz), 7.25(2H, d, J = 7.9 Hz), 7.42(4H, m), 7.90 (2H, d, J = 8.0 Hz), 9.90 (1H, s); IR(cm^{-1}): 3465, 3390, 3030, 2975, 1670, 1595, 1510, 1293, 1225, 1085, 1020, 1007, 860, 690, 517. EIMS, 70Ev, *m/z*: 317 (M^+); Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41; Found: C, 79.51; H, 6.07; N, 4.36%.

3-(4-chlorophenylamino)-1-phenyl-3-p-tolylpropan-1-one (**9**): ^{1}H NMR(200 MHz, $CDCl_3$):1.89(3H, s) 3.41(2H, m), 4.91(1H, t, J = 6.3 Hz), 6.47(2H, d, J = 7.5 Hz), 6.69(1H, t, J = 7.1 Hz), 7.10(2H, m), 7.25(2H, d, J = 8.8 Hz), 7.40(4H, m), 7.90 (2H, d, J = 8.8 Hz); IR(cm^{-1}): 3392, 3024, 1670, 1597, 1514, 1295, 1225, 1082, 1023, 1002, 865, 694, 514. EIMS, 70Ev, *m/z*: 349 (M^+); Anal. Calcd for $C_{22}H_{20}ClNO$: C, 75.53; H, 5.76; N, 4.00; Found: C, 75.45; H, 5.78; N, 4.07%.

3-(4-chlorophenylamino)-3-(4-nitrophenyl)-1-phenylpropan-1-one (**10**): ^{1}H NMR(200 MHz, $CDCl_3$): 3.50(2H, d, J = 6.5 Hz), 4.97(1H, t, J = 6.5 Hz), 6.50(2H, d, J = 7.5 Hz), 6.70(2H, t, J = 7.5 Hz), 7.20(2H, t, J = 7.5 Hz), 7.50–7.80(5H, m), 7.95(2H, d, J = 8.0 Hz); IR(cm^{-1}): 3397, 3040, 2975, 1679, 1598, 1518, 1365, 1305, 1265, 1110, 1072, 860, 694, 513. EIMS, 70Ev, *m/z*: 380 (M^+); Anal. Calcd for $C_{21}H_{17}ClN_2O_3$: C, 66.23; H, 4.50; N, 7.36; Found: C, 66.25; H, 4.53; N, 7.32%.

3-(4-chlorophenylamino)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**11**): ^{1}H NMR(200 MHz, $CDCl_3$): 3.43(2H, d, J = 6.1 Hz), 3.75(3H, s), 4.92(1H, m), 6.45(2H, d, J = 7.7 Hz), 6.60(1H, m), 7.10(2H, t, J = 8.0 Hz), 7.39–7.55(5H, m), 7.68(1H, m), 7.73(2H, d, J = 8.1 Hz); IR(cm^{-1}): 3390, 3035, 2970, 1673, 1595, 1514, 1297, 1225, 1081, 1008, 860, 694, 513. EIMS, 70Ev, *m/z*: 365 (M^+); Anal. Calcd for $C_{22}H_{20}ClNO_2$: C, 72.22; H, 5.51; N, 3.83; Found: C, 72.18; H, 5.56; N, 3.88%.

3-(4-chlorophenylamino)-3-(4-hydroxyphenyl)-1-phenylpropan-1-one (12): ^{1}H NMR(200 MHz, $CDCl_3$): 3.46(2H, m), 4.91(1H, m), 6.51(2H, d, J = 7.9 Hz), 6.65(1H, m), 7.15(2H, m), 7.30(1H, d, J = 7.1 Hz), 7.40(2H, m), 7.55(2H, m), 7.68(1H, d, J = 7.8 Hz), 7.75(2H, d, J = 7.8 Hz), 9.75(1H, s); IR(cm^{-1}): 3457, 3391, 3030, 2972, 1670, 1592, 1514, 1293, 1220, 1080, 1026, 1002, 860, 694, 512. EIMS, 70Ev, *m/z*: 351 (M^+); Anal. Calcd for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98; Found: C, 71.62; H, 5.12; N, 3.95%.

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