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Three-component Mannich-type reactions by bromotriphenylphosphonium bromide catalyst

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Abstract : Bromotriphenylphosphonium bromide catalyzes Mannich-type reactions in a variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones in three-component reactions to afford the corresponding β-amino carbonyl compounds. The catalyst BTPPB depletes water which was produced by the reversible reaction. The salient features of this protocol are shorter reaction time, simplicity of the procedure, good to excellent yields, avoidance of aqueous workup and column-chromatographic separations. The supramolecular structure of the compound 4j was discussed.

Keywords : Bromotriphenylphosphonium bromide; β-amino carbonyl compounds; X-ray; Mannich-type reaction; Catalyst.

INTRODUCTION

The β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products,[1] and widely application in organic synthesis. Hence, there remains a wide scope for the development of convenient methods in the synthesis of β-amino carbonyl compounds. The Mannich-type reactions are classic methods for the preparation of β-amino carbonyl compounds, including β-amino esters, so they are very important for carbon-carbon bond-forming reactions in organic synthesis[2]. These type of reactions have been extensively used as a key step in the synthesis of various natural products as well as in medicinal chemistry[3]. Numerous methods have been reported for the synthesis this kind of compounds by either indirect-type or direct-type Mannich reactions. Recently, direct-type Mannich reactions of aldehydes, enolizable ketones and aryl amines in the presence of various catalysts such as $NbCl_5$,[4] $Zn(OTf)_2$,[5] silica sulfuric acid,[6] $Yb(OPf)_3$,[7] $[NaBArF_4]$,[8] $ZrOCl_2 \cdot 8H_2O$,[9] etc. have been reported. However, these methods suffer from some disadvantages, such as requirements for expensive catalysts, long reaction time or/and atmosphere sensitive reagents. The synthetic method of one-pot, multicomponent, tandem, domino etc. reaction is also pursued by work-

ers.[10] Herein, we report a simple and effective methodology for one-pot, three-component, Mannich-type reactions of aromatic aldehydes, aromatic amines, and enolizable ketones in the presence of bromotriphenylphosphonium bromide (BTPPB).

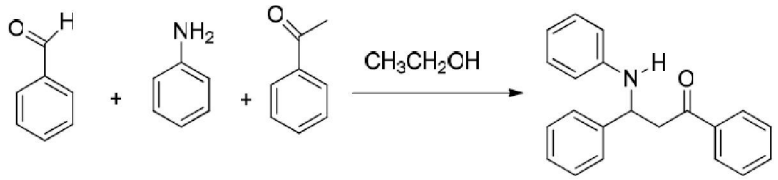
RESULTS AND DISCUSSION

Synthesis

Our initial experiments were carried out using benzaldehyde 1a, 4-nitroaniline 2a and acetophenone 3a in alcohol at room temperature. Several per-bromide compounds, bromopyridinium bromide, bromotriethylaminium bromide and BTPPB were investigated (shown in Scheme 1). It was observed that BTPPB more active than bromopyridinium bromide (need longer reaction time) and bromotriethylaminium bromide. Using 10 mol % BTPPB could give β-amino carbonyl compound 4a in good yield (61%).

A variety of aromatic amines, the aromatic aldehydes and an enolizable carbonyl compounds was examined under the optimized conditions (TABLE 1).

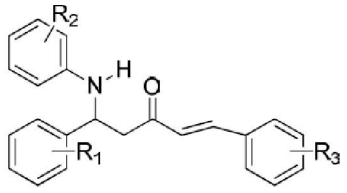
Likewise, benzalacetone also reacted under the same experimental conditions and provided the



1a 2a 3a

Scheme 1 : Selected screening results for Mannich-type reactions; *Catalyst = BTPPB (10%mol), yield 61%, reaction time: 3h; bromotriethylaminium bromide (10%mol), yield 32%, reaction time:24h; bromopyridinium bromide (10%mol), yield 58%,reaction time: 5h.

TABLE 1 : The BTPPB catalyzed direct three-component mannich-type reactions of various aromatic aldehydes, amines and an enolizable carbonyl compound



4m-p

Entry	R^1	R^2	R^3	Time	Yield	Ref.
4a	H	4-NO_2	H	3h	61%	11
4b	H	3-Cl	H	3h	57%	11
4c	4-NO_2	H	H	5h	58%	11
4d	4-NO_2	3-Cl	H	1h	60%	12
4e	3,4,5-tri(-OMe)	3-Cl	H	3h	72%	new
4f	3,4-Methylen edioxy	3-Cl	H	10h	68%	new
4g	4-Cl	4-NO_2	H	5h	36%	13
4h	H	4-NO_2	4-NO_2	3h	34.3%	14
4i	H	3-Cl	4-NO_2	3h	55.3%	15
4j	4-NO_2	3-Cl	4-NO_2	2h	44.7%	new
4k	4-Cl	4-NO_2	4-NO_2	3h	47%	14
4l	4-NO_2	4-NO_2	4-NO_2	8h	40%	new

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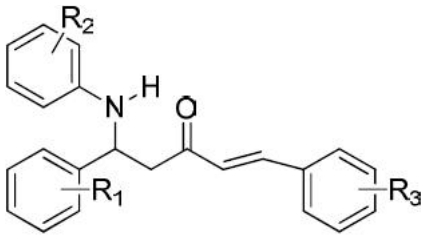
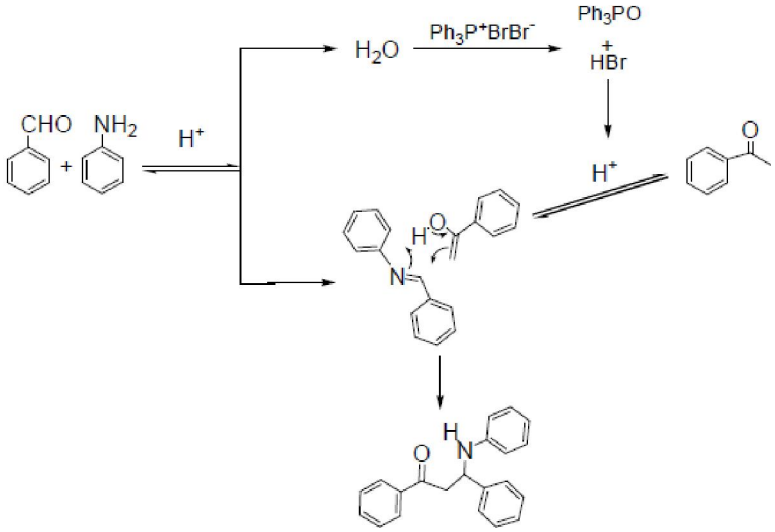
TABLE 2 : Three-component direct Mannich-type reactions of various aromatic aldehydes, amines and benzalacetone under BTPPB catalyzed



Entry	R^1	R^2	R^3	Time	Yield	Ref.
4m	H	4-NO_2	H	1h	76%	16
4n	H	3-Cl	H	10h	45%	16
4o	4-NO_2	4-NO_2	H	12h	57%	new
4p	4-Cl	4-NO_2	H	5h	75.3%	new



Scheme 2 : Plausible mechanistic illustration of BTPPB-catalyzed Mannich-type reactions

corresponding *β*-amino carbonyl compound. It is shown in TABLE 2.

Mechanism

The mechanism of the Mannich reaction has been extensively investigated: The reaction can proceed under both acidic and basic conditions, but acidic conditions are more common. Under acidic conditions, the first step of the reaction is the amine and the protonated non-enolizable carbonyl compound to afford a hemiaminal, and then loses a molecule of water to produce a electrophilic iminium ion. Then the iminium ion reacts with the enolized carbonyl compound (nucleophile) at its α-carbon by an *aldol-type reaction* to afford the Mannich base[17], but all steps are reversible reaction.

The catalyst BTPPB is not an expensive atmosphere sensitive, reagent. We believe that BTPPB catalyzes this kind of conversion through the rapid formation of imines, along with its simultaneous transformation into Ph_3PO and HBr, meanwhile water was depleted in the previous step produced. In the presence of HBr, the enolizable ketones react with the imines to afford the *β*-Amino carbonyl compounds. (Scheme 2)

Crystal structure

The structure of the *β*-amino carbonyl compound 4j is unambiguously supported by an X-ray crystal structure analysis (Figure 1.)[18].

The structure of title compound was identified by X-ray diffraction. Compound, $C_{20}H_{18}N_6O$, Mr= 425.82, crystallizes in the triclinic space group P-1 with unit cell parameters a= 7.2407(19), b=

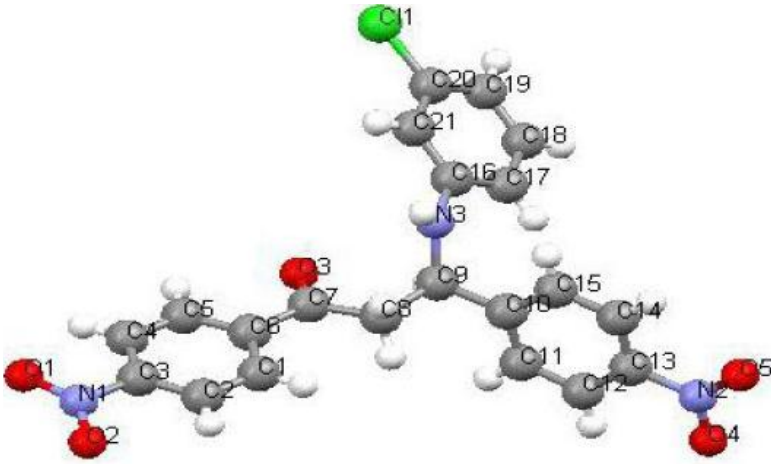


Figure 1 : ORTEP diagram of the compound 4j showing 50% thermal ellipsoids

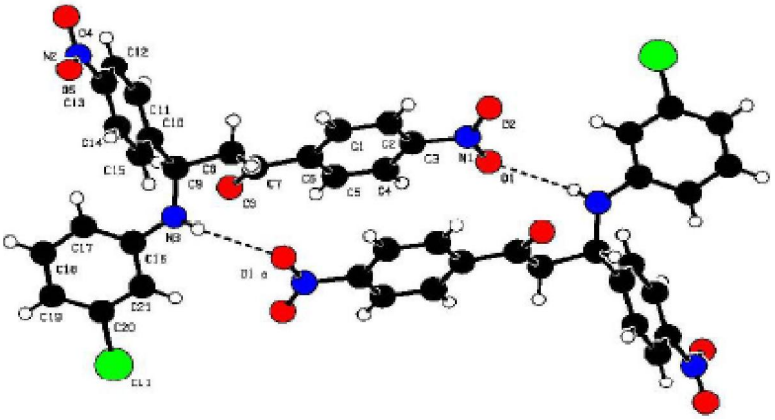


Figure 2 : The H-bond structure of the compound 4j (PWT drawing for the Platon)

9.081(2), c= 16.254(4)Å, α= 96.968(3), β= 96.849(3), γ= 106.271(3)°, V= 1005.1(4)Å^3, Z= 2, Dx= 1.407 mg/cm^3. The final R was 0.0667.

Supramolecular H-bond of compound 4j

These are the interactions of hydrogen bond on the molecular stacking [N3-H3 0.86 H3-O1 2.52 N3-H3···O1 3.124(4)ú, 128.00Ú]. The supramolecular H-bond structure of the compound 4j is shown in Figure 2.

CONCLUSION

The BTPPB first applied as catalyst to the Mannich-type reactions and we also demonstrate the efficacy and generality of BTPPB as a versatile catalyst for the synthesis of ²-amino carbonyl compounds. A variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones have examined to generate the *â*-amino carbonyl compounds. The salient features of this protocol are: (a) the simplicity of the procedure, (b) the ready accessibility of the catalyst and its cost effectiveness, (c) to deplete water which was given by reaction and improves reversible to trend yield, (d) the avoidance of column chromatography.

EXPERIMENTAL

General procedure to prepare the Bromotriphenylphosphonium bromide: Triphenylphosphine[19]

The BTPPB catalyzed direct three-component mannich-type reactions of various aromatic aldehydes, amines and an enolizable carbonyl compound.

Bromotriphenylphosphonium bromide(0.2mmol) was added to a mixture of 1a (2mmol), 2a (2mmol) and 3a (2mmol) in 5ml dry ethanol, and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After the reac-

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tion was completed, the crude solid was filtered off and washed with a mixture solvent of petroleum ether/ethanol (4:1), and dried under the vacuum. Target compound 4a was given by the recrystal of the crude product in hot ethanol.

4e: 3-(3-Chlorophenylamino)-3-(3,4,5-trimethoxyphenyl)-1-phenylpropan-1-one

yield 72%. light yellow solid. m.p 129-130 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 3.423(d, *J* = 4.2Hz, 1H), 3.439(d, *J* = 0.8Hz, 1H), 3.804(d, *J* = 1.6Hz, 9H), 4.706(br, 1H), 4.866(t, *J* = 2 Hz, 1 H), 6.441(dd, *J* = 1.6Hz, *J* = 8Hz, 1H), 6.569(t, *J* = 2Hz, 1H), 6.620(s, 2H), 6.641(dd, *J* = 1.2, *J* = 8Hz, 1H), 6.998 (t, *J* = 8Hz, 1H), 7.435(t, *J* = 8Hz, 2H), 7.558(t, *J* = 8Hz, 1H), 7.878(d, *J* = 8Hz, 1H), 7.871(s, 1H)ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ46.28, 55.39, 56.33, 60.98, 103.43, 112.24, 113.92, 118.08, 128.36, 128.93, 130.29, 133.77, 134.98, 136.90, 137.49, 138.41, 148.43, 153.83, 198.37ppm. MS (m/z, %) [M+, 425] (M+, 7), 306(56), 267(22), 127(31), 105(100), 77 (44). IR (KBr) cm^{-1}, 3357, 1676, 1596, 1464, 1342, 1126, 1037. Anal. Calcd for $C_{24}H_{24}ClNO_4$: C, 67.68; H, 5.68; N, 3.29; Found: C, 67.78; H, 5.88; N, 15.02.

4f: 3-(3-Chlorophenylamino)-3-(benzo[d][1,3]dioxol-5-yl)-1-phenylpropan-1-one

yield 68%. white solid, m.p 122-12 °C. ^{1}H NMR(400MHz, $CDCl_3$): δ 3.430(m, 2H), 4.685(br, 1H), 4.862(dd, *J* = 5.2Hz, *J* = 7.2Hz, 1H), 5.887(dd, *J* = 1.2Hz, *J* = 4Hz, 2H), 6.429(dd, *J* = 2 Hz, *J* = 8Hz, 1H), 6.537(t, *J* = 2Hz, 1H), 6.620(dd, *J* = 1.2Hz, *J* = 8Hz, 1H), 6.731(d, *J* = 8Hz, 1H), 6.872 (td, *J* = 1.6Hz, *J* = 8Hz, 2H), 6.972(t, *J* = 8Hz, 1H), 7.427 (t, *J* = 8Hz, 2H), 7.548(t, *J* = 8Hz, 1H), 7.878(d, *J* = 8Hz, 1H), 7.870(s, 1H)ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ 46.39, 54.82, 101.27, 106.88, 108.72, 112.37, 113.94, 118.08, 119.75, 128.38, 128.93, 130.27, 133.75, 134.95, 136.44, 136.74, 147.11, 148.09, 148.33, 198.24ppm. MS: (m/z, %) [M+, 379] (M+,7), 260(80), 252(29), 127(26), 105(100), 77 (45). IR (KBr) cm^{-1}, 3380, 1670, 1598, 1485, 1445, 1244, 1039. Anal. Calcd for $C_{22}H_{18}ClNO_3$: C, 69.57; H, 4.78; N, 3.69; Found: C, 69.67; H, 4.88; N, 3.72.

4j:3-(3-Chlorophenylamino)-1,3-bis(4-nitrophenyl)propan-1-one

yield 44.7%, yellow solid, m.p 113-114 °C, ^{1}H NMR (400MHz, $CDCl_3$): δ 3.510(m, 2H), 4.623(br, 1H), 5.139(t, *J* = 6Hz, 1H), 6.414(dd, *J* = 2Hz, *J* = 8Hz, 1H), 6.29(t, *J*= 2Hz, 1H), 6.687(dd, *J* = 0.8Hz, *J* = 8Hz, 1H), 7.023(t, *J* = 8Hz, 1H), 7.622(d, *J* = 8Hz, 2H), 8.058(d, *J* = 8.8Hz, 2H), 8.190(d, *J* = 8Hz, 2H), 8.297(d, *J* = 8.8Hz, 2H) ppm. ^{13}C NMR (100MHz, $CDCl_3$):δ46.22, 53.88, 112.25, 113.96, 118.96, 124.29, 124.49, 127.63, 129.40, 130.60, 135.31, 140.71, 147.43, 147.69, 149.64, 150.91, 195.76ppm. MS (m/z, %) [M+, 425] (M+, 2), 306(23), 281(100), 251(86), 127(65), 105(46), 76(42). IR (KBr) cm^{-1}, 3378, 1692, 1597, 1520, 1345, 1320, 1198. Anal. Calcd for $C_{21}H_{16}ClN_3O_5$: C, 59.23; H, 3.79; N, 9.87; Found: C, 59.33; H, 3.67; N, 9.77.

4l:3-(4-Nitrophenylamino)-1,3-bis(4-nitrophenyl)propan-1-one

yield 40%, yellow solid, m.p 191-192 °C. ^{1}H NMR (400MHz, DMSO): δ 3.624(dd, *J* = 3.2Hz, *J* = 18Hz, 1H), 3.895(m, 1H), 5.357(s, 1H), 6.648 (d, *J* = 8.8Hz, 1H), 7.787(d, *J* = 8.4Hz, 2H), 7.856(d, *J* = 6.4Hz, 1H), 7.964(d, *J* = 8.8Hz, 2H), 8.241(d, *J* = 6.8Hz, 4H), 8.360(d, *J* = 8.4Hz, 2H) ppm. ^{13}C NMR (100MHz, DMSO):δ45.82, 51.73, 111.60, 123.74, 123.81, 125.99, 128.00, 129.48, 136.49, 140.84, 146.78, 149.99, 150.28, 153.19, 195.36ppm. MS (m/z, %) [M+, 436] (M+, 0.5), 281(100), 251(76), 176(34), 138(65), 108(30), 76(36), 65(55). IR (KBr) cm^{-1}, 3400, 1688, 1597, 1519, 1347, 1310, 1113. Anal. Calcd for $C_{21}H_{16}N_4O_7$: C, 57.80; H, 3.70; N, 12.84; Found: C, 57.99; H, 3.65; N, 12.88.

4o:(E)-5-(4-Nitrophenylamino)-5-(4-nitrophenyl)-1-phenylpent-1-en-3-one

yield 57%, yellow solid. m.p 179-180 °C. ^{1}H NMR (400MHz, DMSO): δ 3.188(dd, *J* = 4.4Hz, *J* = 17.2Hz, 1H), 3.466(m, 1H), 5.325(m, 1H), 6.670(d, *J* = 8.8Hz, 2H), 6.989(d, *J* = 16.4Hz, 1H), 7.447(t, *J* = 2.8Hz, 3H), 7.676(d, *J* = 16.4Hz, 1H), 7.729(m, 3H), 7.758(d, *J* = 8.8Hz, 1H), 7.874(d, *J* = 7.2Hz, 1H), 7.957(d, *J* = 9.2Hz, 2H), 8.236(d, *J* = 8.8Hz, 2H)ppm. ^{13}C NMR (100MHz,

DMSO):δ47.17, 51.91, 111.71, 123.73, 125.96, 126.11, 127.90, 128.45, 128.94, 130.58, 134.29, 136.43, 142.86, 146.70, 150.56, 153.22, 196.02ppm. MS (m/z, %) [M+, 417] (M+, 4.4), 278(100), 162(50), 138(61), 103(62), 77(43), 65(58). IR (KBr) cm^{-1}, 3431, 3334, 1689, 1608, 1518, 1309, 1287, 1114. Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07; Found: C, 66.22; H, 4.66; N, 10.12.

4p:(E)-5-(4-Nitrophenylamino)-5-(4-chlorophenyl)-1-phenylpent-1-en-3-one

yield 75.3%, yellow solid. m.p 151-152 °C. ^{1}H NMR (400MHz, $CDCl_3$): δ 3.211(m, 2H), 4.991(t, *J* = 6Hz, 1H), 5.652(br, 1H), 6.487(dd, *J* = 3.2Hz, *J* = 12Hz, 2H), 6.655(d, *J* = 16.4Hz, 1H), 7.363(m, 4H), 7.401(m, 3H), 7.488(m, 3H), 7.988(d, *J* = 9.2Hz, 2H)ppm. ^{13}C NMR (100MHz, $CDCl_3$): δ 47.39, 54.03, 112.47, 125.93, 126.39, 127.84, 128.72, 129.28, 129.48, 131.35, 133.87, 134.06, 138.81, 139.79, 144.82, 152.15, 197.66ppm. MS (m/z, %) [M+, 406] (M+, 7.5), 267(100), 233(34), 138(62), 131(87), 103(81), 77(53), 65(51). IR (KBr) cm^{-1}, 3333, 1686, 1604, 1498, 1308, 1287, 1200, 1113. Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89; Found: C, 67.99; H, 4.78; N, 6.78.

SUPPLEMENTARY DATA

CCDC 918051 contains the supplementary crystallographic data for 4j. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Full experimental details and ^{1}H and ^{13}C NMR, X-ray data of title compounds can be found via the Supplementary Content section of this article's Web page.

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[17] The single crystal of 4j was successfully grown as a racemic mixture from hexane and ether.CCDC 918051 contains the supplementary crystallographic data for compound 4j, These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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