An Expedient Three-Component Approach to the Synthesis of α,α-Disubstituted Amines under Barbier-like Conditions

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Abstract: A series of α,α-disubstituted amines such as diarylmethylamines, 1,2-diarylethylamines, and amino esters have been prepared in acetonitrile using a simple and expedient three-component Mannich-type procedure involving organic halides, aldehyde derivatives, and amines. Reactions are conducted under Barbier-like conditions using simple organic halides and zinc dust for the in situ generation of organozinc reagents.

Key words: amines, halides, multicomponent reactions, organometallic reagents, zinc

Multicomponent reactions constitute an attractive and powerful tool of modern organic chemistry, allowing the formation of complex structures in a single-step procedure.[1] One of the most renowned multicomponent procedures is the Mannich reaction,[2] which allows the straightforward formation of numerous nitrogen-containing backbones. Accordingly, in the past decade, there has been tremendous progress in the development of asymmetric versions of the Mannich reaction for the synthesis of nitrogen-containing molecules such as α-amino acid derivatives,[3] β-amino carbonyl compounds,[4] or amino alcohols.[5] Some other modern variants of the Mannich reaction feature preformed organometallic reagents like dialkylzinc as nucleophiles besides the amine and the aldehyde derivative.[6] However, the in situ formation of organometallic intermediates under Barbier-like conditions has been the subject of a significant interest during the last past years owing to the versatility, the simplicity and the cost-effectiveness of such procedures which were principally applied to the synthesis of propargylic amines.[7] Recently, Fan and co-workers described the efficient three-component reaction of allyl or benzyl bromide with primary amines and aldehydes in THF resulting in the formation of several α,α-disubstituted amines.[8] However, this work was limited to the use of allyl and benzyl bromide as starting halides and moreover, the use of secondary amines was not mentioned.

As part of our program devoted to the arylation at the position α to the nitrogen, we recently reported a Mannich-type three-component procedure allowing the preparation of diarylmethylamines in acetonitrile, starting from preformed arylzinc compounds, secondary amines, and aldehydes.[9] Apart from this main purpose, it was also disclosed the possibility to operate under Barbier-like conditions, by means of a cobalt-catalyzed zinc-mediated three-component coupling.[9b] Herein, we both confirm the possible in situ activation of aryl halides and further extend the procedure by reporting several examples of one-pot reactions applied to the synthesis of α,α-disubstituted amines like diarylmethylamines, 1,2-diarylethylamines, and even amino esters.

With the ultimate goal to set up a useful three-component method for the synthesis of various nitrogen derivatives, we took as a starting point our previous studies dealing with the use of preformed organozinc reagents in three-component couplings with aldehydes and amines,[9] and envisaged to simplify the procedure by operating under Barbier-like conditions. It was expected that such a modification of the procedure might be realizable provided that the in situ formation of both organozinc reagents and reactive nitrogen-containing intermediates (imines or iminium ions equivalents) proceeds concomitantly. Indeed, in such a case, the creation of the expected carbon–carbon bond would likely happen instantly thus limiting risks of byproduct formation. The relevance of this hypothesis was supported by the fact that in acetonitrile such organometallic formations are generally exothermic. This thermal activation usually procures a positive outcome in the simultaneous formation of electrophilic nitrogen-containing intermediates and their trapping by the organozinc reagent. Moreover, in the case of less reactive organic halides, we envisaged an external heating to both accelerate the formation of the organozinc reagent and its addition to the formal C=N double bond.

A preliminary survey of three-component Barbier-type couplings involving benzyl bromide as a model organic halide revealed that reactions proceed very fast in acetonitrile compared to related THF solutions.[10] It was also observed that at least two equivalents of the organic halide are necessary for the reaction to occur.[11] This result accounts for an acid–base reaction between the intermediate hemiaminal and the in situ generated organozinc reagent leading to a zinc-associated α-amino alcoholate which is displaced by a further equivalent of the organozinc compound. A possible mechanism for such a process has already been described elsewhere.[8]

In a typical experiment, zinc dust was placed in anhydrous acetonitrile and activated using trifluoroacetic acid in the

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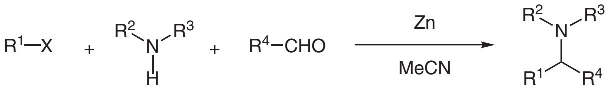
presence of a limited amount of the organic halide (0.4 mL). After five minutes at room temperature, the aldehyde and the amine were added along with the organic halide in the mixture. An exothermic reaction soon occurred resulting in an important rise of the medium temperature (ambient to 50–60 °C), which was not controlled using a water bath. The resulting solution was stirred for one hour at ambient temperature and the reaction was then quenched with a saturated ammonium chloride solution. A classical workup followed by a chromatographic purification over neutral alumina afforded the expected compound.[12] In the case of aryl bromides, which require catalysis to be converted into the related organozinc reagents,[13] cobalt bromide was added to the reaction mixture before the introduction of substrates. Results are reported in Table 1.

Table 1 Three-Component Synthesis of α,α-Disubstituted Amines under Barbier-like Conditions[a]



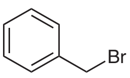
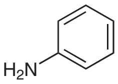
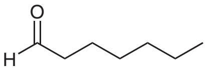
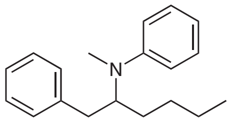
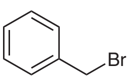
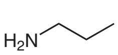
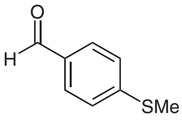
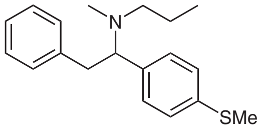
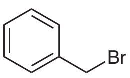
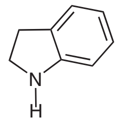
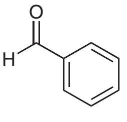
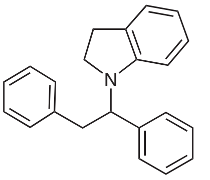
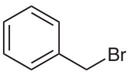
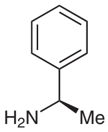
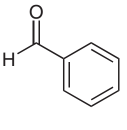
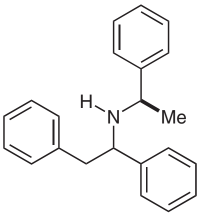
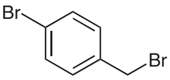
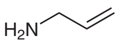
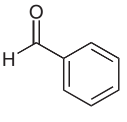
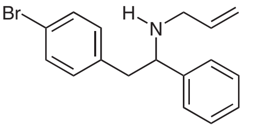
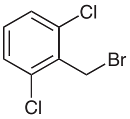
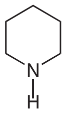
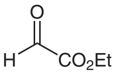
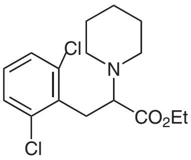
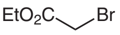
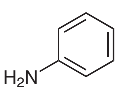
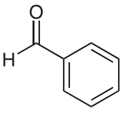
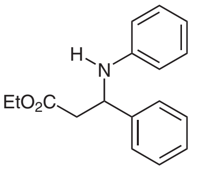
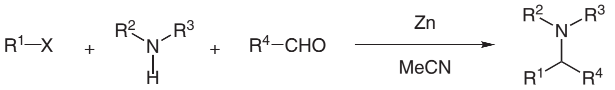
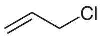
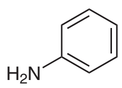
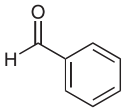
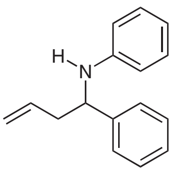
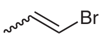
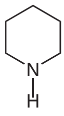
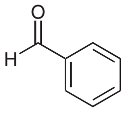
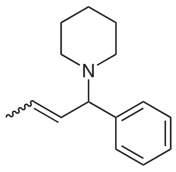
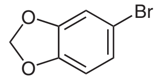
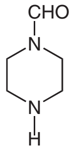
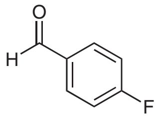
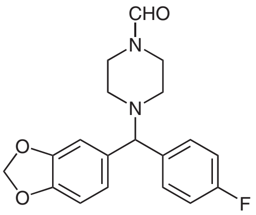
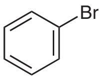
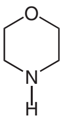
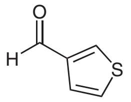
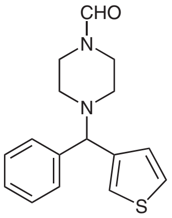
Entry	Organic halide	Amine	Aldehyde	Additional conditions	Time (h)	Product	Isolated yield (%)
1				–	1	 **1**	79
2				–	0.5	 **2**	70
3				–	0.5	 **3**	74
4				–	1	 **4**	58[b]
5				–	1	 **5**	65
6				–	1	 **6**	87
7[c]				–	18	 **7**	55

Table 1 Three-Component Synthesis of α,α-Disubstituted Amines under Barbier-like Conditions[a] (continued)



Entry	Organic halide	Amine	Aldehyde	Additional conditions	Time (h)	Product		Isolated yield (%)
8				DMF, Bu$_4$NI 60 °C[d]	18		**8**	50
9[c]				CoBr$_2$, ZnBr$_2$ 60 °C[e]	1		**9**	81
10				CoBr$_2$, ZnBr$_2$ 60 °C[e]	2		**10**	70
11				CoBr$_2$, ZnBr$_2$ 60 °C[e]	2		**11**	80

[a] Typical experimental conditions: anhyd MeCN (40 mL), Zn dust (2.7 g, 40 mmol), amine (10 mmol), aldehyde derivative (11 mmol), organic halide (25 mmol).

[b] Yield for a mixture of diastereomers: dr = 75:25.

[c] Caution: vigorous reaction.

[d] DMF (5 mL) and Bu$_4$NI (3.69 g, 10 mmol) were also used. The reaction mixture was heated at 60 °C for 18 h.

[e] Cobalt bromide (0.66 g, 3 mmol) and zinc bromide (0.68 g, 3 mmol) were also used. The reaction mixture was heated at 60 °C for 2 h.

Aromatic aldehydes, as well as an aliphatic aldehyde (entry 1), undergo the coupling. It should be noted that ethyl glyoxylate allows the three-component coupling in excellent yield (entry 6). This result is of particular significance for a further extension to the synthesis of non-natural α-amino acid derivatives. Various amines are efficient in the coupling and it is interesting to observe that aromatic amines react as well as aliphatic amines. The cyclic character of the amine has no impact on the coupling and the reaction performs well with both primary and secondary amines. Benzyl bromides (entries 1–6) react faster than other organic halides (entries 7–11), which sometimes require additional heating to undergo the coupling. It is worth noting that aryl bromides react efficiently in the presence of a substoichiometric amount of cobalt bromide provided that a moderate heating is applied to the reaction mixture (entries 10, 11). This result is of particular significance since it appears, to the best of our knowledge, as unprecedented examples of Mannich-type reactions involving simple aryl bromides as starting compounds and consequently, a separate study has been undergone in order to determine the scope and limitations of this particular reaction.

We also experimented with the use of an α-bromoester in the procedure (entry 7). In that case, we did not remark any important competition between the three-component coupling (which is the almost sole reaction pathway) providing the β-amino ester **7**, and the Reformatsky-type addition to the carbonyl compound furnishing an alcohol. Furthermore, contrary to other authors,[14] we did not observe a substantial formation of β-lactam by subsequent cyclization of **7**.

In standard reaction conditions, alkyl halides like 1-bromoheptane and 1-iodooctane do not solely undergo the three-component coupling. The formation of various byproducts by Würtz-like dimerization of the alkyl halide or a further N-alkylation of the three-component nitrogenated product (when a primary amine is employed) could also be established upon analysis of the reaction mixture.

We also realized an experiment using a mixture of (*Z*)- and (*E*)-1-bromoprop-1-ene as starting compound (entry 9). Regarding the chemical structure of this substrate, we chose to use the conditions analogous to those employed for the three-component coupling of aryl bromides. In that case, an almost quantitative reaction is observed, with no significant sign of disparity between the reactivity of both stereoisomers, a mixture of *E* and *Z* three-component coupling products being detected in the reaction mixture. However, we could observe some slight fluctuations in the stereoisomeric ratio of coupling products, with respect to reaction time and/or temperature. This might indicate that a stereoisomer is slightly more reactive than the other. A further supplementary survey involving pure stereoisomers could provide more indications about this observation.

During the course of our preliminary investigation, we noticed that the reaction cannot be conducted in acetonitrile starting from allyl bromide which reacts vigorously following an exothermic reaction leading to the production of volatile material, probably by a Würtz-like dimerization of allyl bromide. Interestingly, allyl chloride reacts smoother than allyl bromide, under thermal assistance and in the additional presence of DMF and Bu_4NI (entry 8).[15] Under the experimental conditions described by Fan and co-workers,[8] allyl bromide was efficient in such couplings, conducted in THF at room temperature for several hours (typically 12–24 h). If one considers that our procedure involving acetonitrile as the solvent leads generally to exothermic reactions which are completed in less than one hour and that, in addition, zinc-mediated chemical syntheses of arylzinc compounds cannot be conducted in THF solutions instead of acetonitrile,[13] it appears that the nature of the solvent has a great influence over the reaction rate and that THF globally slows down the above-mentioned processes compared to acetonitrile. In order to define the reasons for which the solvent is of so crucial importance, we envisage to implement a further mechanistic investigation focused on transient organometallic species by means of in situ ReactIR measurements and electroanalytical investigations, which have already provided conclusive results on related systems.[16]

In conclusion, the results reported in this preliminary study prove that straightforward three-component reactions between various organic halides, primary or secondary amines, and aldehyde derivatives can be conducted in Barbier-like conditions. Consequently, we found a very promising reaction system, able to provide a wide variety of nitrogen-containing products under convenient reaction conditions. Further developments, especially with aryl bromides as starting compounds, are currently in progress.

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References and Notes

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(10) During the course of a previous work dealing with the synthesis of benzylzinc bromide (nonpublished results), we could observe that the reaction is more rapid in MeCN than in THF (>2 times faster). Additionally, it was observed by Gosmini et al. that the solvent is of crucial importance in the cobalt-catalyzed synthesis of arylzinc halides, which cannot be conducted in THF (see ref. 13 for details).

(11) This is consistent with previous works demonstrating that organozinc reagents have to be used in sufficient excess (>2 equiv) to react efficiently with aldehydes and amines (see ref. 9 for details).

(12) Coupling products were characterized using ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$), mass spectrometry, and when useful ^{19}F NMR (376 MHz, $CDCl_3$), and IR spectroscopy.

Data for Selected Compounds *N*-(1-Phenyloctan-2-yl)-aniline (1)

Colorless oil; yield 2.21 g (79%). ATR-FTIR (neat): 3405, 3025, 2926, 2855, 1600, 1504, 792, 691 cm^{-1}. ^{1}H NMR: δ = 7.41–7.29 (m, 7 H), 6.79 (t, *J* = 7.3 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 2 H), 3.75–3.73 (m, 1 H), 3.58 (br s, 1 H), 2.97 (dd, *J* = 13.6,4.6 Hz, 1 H), 2.91 (dd, *J* = 13.6, 6.4 Hz, 1 H), 1.69–1.40 (m, 10 H), 0.97 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR: δ = 147.7, 138.7, 129.7, 129.5, 128.4, 126.3, 117.0, 113.2, 53.7, 40.2, 34.2, 31.9 29.4, 26.2, 22.7, 14.2. MS: *m/z* (%) = 191 (13), 190 (100), 118 (9), 106 (39), 91 (6), 55 (6). Anal. Calcd for $C_{20}H_{27}N$: C, 85.35; H, 9.67; N, 4.98. Found: C, 85.68; H, 9.99; N, 4.57.

Allyl-[2-(4-bromo-phenyl)-1-phenyl-ethyl]-amine (5)

Yellow oil; yield 2.05 g (65%). ATR-FTIR (neat): 3324, 3062, 3025, 2919, 2833, 1642, 1487, 1453, 1071, 1011, 915, 803, 756, 699 cm^{-1}. ^{1}H NMR: δ = 7.40–7.26 (m, 7 H), 6.99 (d, *J* = 7.9 Hz, 2 H), 5.76–5.88 (m, 1 H), 5.09–5.05 (m, 2 H), 3.90 (t, *J* = 7.0 Hz, 1 H), 3.14 (dd, *J* = 14.2, 4.7 Hz, 1 H), 3.01 (dd, *J* = 14.2, 6.5 Hz, 1 H), 2.92 (d, *J* = 6.8 Hz, 2 H), 1.50 (br s, 1 H). ^{13}C NMR: δ = 143.1, 137.7, 136.7, 131.4, 131.1, 128.4, 127.3, 127.2, 120.2, 115.8, 63.7, 50.0, 44.5. MS: *m/z* (%) = 179 (5), 178 (6), 165 (5), 147 (11), 146 (100), 129 (8), 104 (7), 91 (35), 90 (8), 89 (5). Anal. Calcd for $C_{17}H_{18}BrN$: C, 64.57; H, 5.74; N, 4.43. Found: C, 64.30; H, 5.75; N, 4.30.

Ethyl (*N*-Phenylamino)-3-phenylpropionate (7)

Pale yellow solid; yield 1.48 g (55%); mp 71–73 °C. ATR-FTIR (neat, cm^{-1}): 3384, 3025, 2980, 2925, 1712, 1602, 1218, 760, 689. ^{1}H NMR: δ = 7.42 (d, *J* = 7.5 Hz, 2 H), 7.36 (t, *J* = 7.3 Hz, 2 H), 7.28 (t, *J* = 7.0 Hz, 1 H), 7.14 (t, *J* = 7.6 Hz, 2 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 6.60 (d, *J* = 7.8 Hz, 2 H), 4.87 (t, *J* = 6.6 Hz, 1 H), 4.64 (br s, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 2.84 (d, *J* = 6.2 Hz, 2 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR: δ = 171.2, 146.8, 142.2, 129.2, 128.8, 127.5, 126.3, 117.8, 113.7, 60.8, 55.0, 42.9, 14.2. MS: *m/z* (%) = 269 (20), 183 (14), 182 (100), 180 (9), 104 (17), 77 (6). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.65; H, 7.05; N, 5.07.

(13) The efficient chemical synthesis of arylzinc reagents has been described in acetonitrile starting from aryl bromides and using a cobalt-catalyzed process, see: Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867.

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