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Three-Component Synthesis of α-Branched Amines under Barbier-like Conditions

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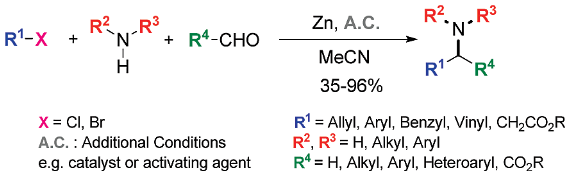

An array of α-branched amines has been prepared by using an expedient three-component Mannich-type reaction among organic halides, aldehyde derivatives, and amines. The experimental procedure, which is characterized by its simplicity, employs zinc dust for the in situ generation of organozinc reagents. We show that this Barbier-like protocol constitutes a useful entry to diarylmethylamines, 1,2-diarylethylamines, α- or β-amino esters, benzylamines, and β-arylethylamines.

Multicomponent reactions (MCRs) do not only constitute efficient tools for parallel synthesis in drug discovery, they also represent a relevant methodology for the preparation of important synthetic intermediates or natural products.[1,2] The probably most renowned non-isocyanide-based MCR is the Mannich reaction,[3] which has been the subject of constant development over the past decades, due to the important synthetic perspectives induced by related processes. Accordingly, some modern variants of the reaction involve the use of additional catalysts to provide rate enhancement and furnish a source of chirality for the stereoselective preparation of useful synthetic intermediates like α-amino acid derivatives,[4] β-aminocarbonyl compounds,[5] or amino alcohols.[6] Concomitantly, other significant developments regarding nucleophile diversification have also been disclosed. Thus, procedures related to the Mannich reaction, employing an electron-rich aromatic compound (aromatic Mannich reaction[7]), an organoboronic acid (Petasis reaction[8]), or a preformed organometallic reagent[9] as the nucleophile, have been used in various synthetic processes. Furthermore, in the latter area, the formation of organometallic intermediates under Barbier-like conditions (in situ metalation of halides or related compounds) has been the subject of significant interest over the last few years owing to the important experimental simplicity and the general efficiency of such procedures.[10]

As part of our work devoted to the development of MCRs involving organometallic reagents, we recently developed a Mannich-type three-component reaction among amines, aldehyde derivatives, and preformed arylzinc or benzylzinc reagents.[11] In a very recent study, we also disclosed the possibility of operating under Barbier-like conditions, starting from organic halides as organozinc precursors.[12] Herein,

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(1) Zhu, J.; Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005.

(2) For recent reviews on MCRs and Asymmetric MCRs (AMCRs), see: (a) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693–700. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980. (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133–1144. (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.

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(9) (a) Desrosier, J.-N.; Côté, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186–6192. (b) Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864–10867. (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410. (d) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244–4247.

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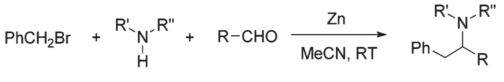
TABLE 1. **Three-Component Reaction between Benzyl Bromide, an Amine, and an Aldehyde**[a]



1a-o

entry	amine	R	time (h)		isolated yield (%)
1	piperidine	Ph	1.5	**1a**	77
2	indoline	Ph	0.5	**1b**	74
3	benzylamine	Ph	1	**1c**	76
4	(*R*)-1-phenylethylamine	Ph	1	**1d**	58 (dr = 75:25)
5	*n*-propylamine	Ph	1	**1e**	86
6	allylamine	Ph	1	**1f**	73
7	aniline	Ph	1	**1g**	89
8	3,5-dimethoxyaniline	Ph	0.5	**1h**	84
9	*n*-propylamine	2-(trifluoromethyl)phenyl	1	**1i**	54
10	*n*-propylamine	4-(methylthio)phenyl	0.5	**1j**	70
11	allylamine	4-fluorophenyl	0.5	**1k**	67
12	allylamine	thiophen-3-yl	0.5	**1*l***	83
13	aniline	*n*-hexyl	1	**1m**	79
14	morpholine	CO_2Et	1	**1n**	83
15	piperidine	H[b]	1	**1o**	90

[a] Experiments were typically conducted with 40 mL of acetonitrile, 3 mL (25 mmol) of benzyl bromide, 11 mmol of the aldehyde derivative, 10 mmol of the amine, and 2 g (30 mmol) of zinc dust, preactivated in the presence of TFA. [b] Paraformaldehyde was used as a formaldehyde synthetic equivalent.

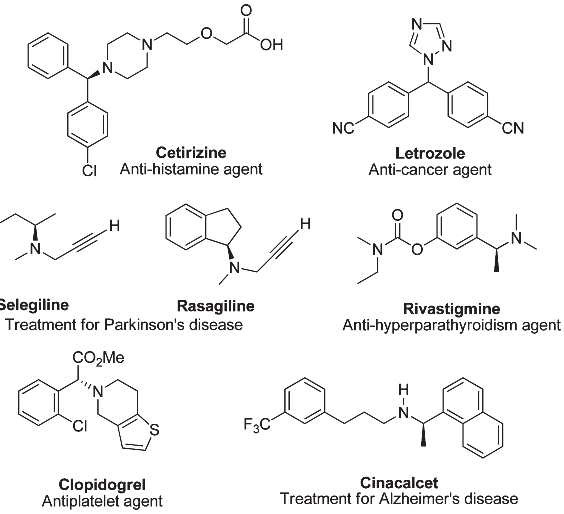


FIGURE 1. Examples of small α-branched amines.

we both confirm the possible metalation of organic halides in situ and further extend the procedure by showing its relevance for the formation of diverse small α-branched amines.

Small α-branched amines are compounds of important therapeutic interest that can be used in a wide array of pharmaceutical applications (Figure 1).

Among the important set of known or conceivable methods for their preparation, we assumed that a multicomponent approach could appear as a useful and general tool for synthesis rationalization. Accordingly, we endeavored to examine synthetic possibilities provided by three-component couplings between organozinc reagents, amines, and aldehyde derivatives and additionally envisage to operate under Barbier-like conditions, thus starting from organic halides and zinc dust as the reductive metal for the in situ generation of the organozinc species. To this end, brominated reagents were chosen as model starting halides with respect to their general proper reactivity or the global cost-efficiency of the process compared to those of chlorinated or iodinated derivatives.

In a first series of experiments, we investigated the scope of the amine and the aldehyde derivative in a three-component coupling with benzyl bromide. Preliminary experiments indicated that the amounts of reagents and the medium temperature were the main reaction parameters. In that context, the most general and convenient reaction conditions were defined as follows: acetonitrile is used as the solvent, zinc dust as the reductive metal, and the halide (2.5 equiv[13]), the amine (1 equiv), and the aldehyde derivative (1.1 equiv) are allowed to react at room temperature (without external control).[14] Under these conditions, reactions generally appeared to be complete in less than 2 h. Results are reported in Table 1.

It can be noticed that an important range of amines undergo the three-component coupling. Indeed, aromatic amines react almost as well as aliphatic amines and the cyclic character of the amine has no impact on the reaction. In addition, the coupling performs well with both primary and secondary amines. Aromatic and heteroaromatic aldehydes (Table 1, entries 1−12), as well as an aliphatic aldehyde (Table 1, entry 13), are efficient in the reaction and it should be noted that ethyl glyoxylate allows the formation of the corresponding three-component product in excellent yield (Table 1, entry 14). As an extension of the process (giving only α-monosubstituted products), paraformaldehyde can also be used as a formaldehyde equivalent to provide a reliable entry to compounds of the β-arylethylamine class (Table 1, entry 15). It should be noted that such a synthesis has already been described, but only starting from preformed benzylzinc reagents so far.[11c,15]

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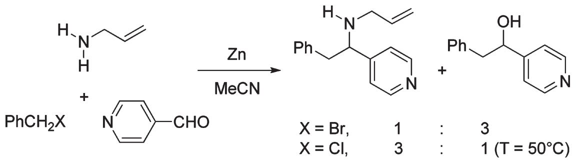
(12) aSengmany, S.; Le Gall, E.; Troupel, M. *Synlett* **2008**, 1031–1035. (b) Haurena, C.; Sengmany, S.; Huguen, P.; Le Gall, E.; Martens, T.; Troupel, M. *Tetrahedron Lett.* **2008**, *49*, 7121–7123.

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

(14) In some cases, the reaction is very exothermic but the rise of the medium temperature might not be controlled by using external cooling, otherwise significantly longer reaction times are observed. However, for safety reasons, a water condenser might be required if the concentration of substrates is increased or if the reaction is conducted on a larger scale.

(15) Ku, Y.-Y.; Grieme, T.; Pu, Y.-M.; Bhatia, A. V.; King, S. A. *Tetrahedron Lett.* **2005**, *46*, 1471–1474.

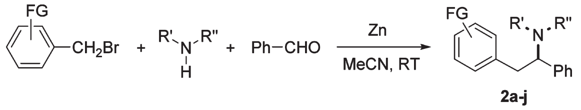
SCHEME 1. Reaction Involving 4-Pyridinecarboxaldehyde



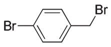
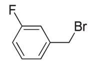
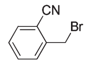
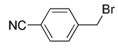
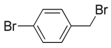
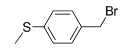
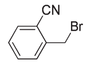
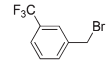
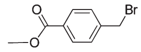
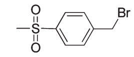
Surprisingly, an experiment involving benzyl bromide, allylamine, and 4-pyridinecarboxaldehyde as the carbonyl derivative did not give rise to the major formation of the three-component coupling product but to the alcohol resulting from the direct addition of the organozinc to the carbonyl in a 1:3 ratio (Scheme 1). This could be partially overcome by using benzyl chloride instead of bromide and by heating the mixture to induce the in situ formation of the organozinc compound. In that case, after several hours at 50 °C, the ratio of products could be inverted showing that the rate of formation of the organozinc reagent can be of crucial importance.

In a second set of experiments, we investigated the scope of functionalized benzyl bromides. To this end, benzaldehyde was chosen as the model aldehyde and the experimental conditions were typically identical with those already described for benzyl bromide as the starting halide. Results are displayed in Table 2.

TABLE 2. Three-Component Reaction between a Functionalized Benzyl Bromide, an Amine, and Benzaldehyde[a]



2a-j

Entry	Benzyl bromide	Amine	Time (h)		Isolated yield (%)
1		Piperidine	3	**2a**	59
2		Piperidine	12	**2b**	35
3		Piperidine	20	**2c**	71
4		*n*-Propylamine	1	**2d**	46
5		Allylamine	1	**2e**	65
6		Aniline	1	**2f**	55
7		Aniline	1	**2g**	96
8		Aniline	2.5	**2h**	72
9		Aniline	1	**2i**	81
10		Aniline	3.5	**2j**	60

[a] Experiments were typically conducted with 20 mL of acetonitrile, 12.5 mmol of the benzyl bromide, 0.55 mL (5.5 mmol) of benzaldehyde, 5 mmol of the amine, and 1 g (15 mmol) of zinc dust, preactivated in the presence of TFA.

Most of the functionalized benzyl bromides react quickly and efficiently with benzaldehyde and a variety of amines. However, some functional groups might present incompatibilities with zinc dust. This is notably the case of the nitro function of 4-nitrobenzyl bromide whose reaction with benzaldehyde and *n*-propylamine led to the three-component product in only 14% yield after 22 h at 50 °C, numerous byproducts being detected in the reaction mixture.

In another series of experiments, we envisaged to engage aryl halides as organozinc precursors. Compared to the experimental conditions reported above, an additional cobalt catalyst ($CoBr_2$) was introduced in the reaction mixture that was also heated (60 °C) in order to favor the in situ conversion of the bromide into the corresponding organozinc compound.[16] Results are reported in Table 3.

Bromobenzene and aryl bromides bearing an electron-donating group react fairly well (Table 3, entries 1−5) whereas those bearing an electron-withdrawing group do not undergo the coupling (Table 3, entries 6 and 7). In these latter cases, the starting bromide proved to remain unchanged, suggesting that the reaction does not start at all. Nevertheless, in the presence of suitable aryl bromides, a heteroaromatic aldehyde (Table 3, entry 4) can be employed in the reaction as well as a substituted benzaldehyde (Table 3, entry 5). An aliphatic aldehyde leads to the formation of a complex mixture of products, probably via base-induced reactions at the position α to the carbonyl (Table 3, entry 8). However, paraformaldehyde reacts efficiently as a formaldehyde equivalent to allow the straightforward formation of benzylamine **3f** (Table 3, entry 9).

As mentioned in a recent paper,[12b] when allowed to react with in situ-generated aromatic organozinc reagents, primary amines did not lead to three-component coupling products. Indeed, imines resulting from the reaction of the amine and the aldehyde are only weak electrophiles. Consequently, a further activation of the C=N bond might be required to observe the addition of arylzinc reagents.

In a last set of experiments, we undertook to examine the scope of miscellaneous halides in the three-component reaction. Results are reported in Table 4.

In both experiments involving benzyl-like bromides (Table 4, entries 1 and 2), a loss of the starting halide upon Würtz-like coupling of the latter is observed. This problem is crucial starting from 9-bromofluorene, which gives rise to the sole formation of 9,9′-bifluorene upon fast reaction with zinc dust. We also tried to use an α-bromoester in the procedure (Table 4, entry 3).[17] In that case, the Reformatsky-type addition of the organozinc reagent to the carbonyl compound was not observed. Furthermore, contrary to other authors, we did not remark the formation of a β-lactam by subsequent cyclization of the β-aminoester **4b**.[18] We could notice that the reaction cannot be conducted starting from allyl bromide, which reacts vigorously, leading to the formation of volatile material (Table 4, entry 4). Interestingly, allyl chloride reacts smoother than allyl bromide, under thermal assistance and in the additional presence of DMF

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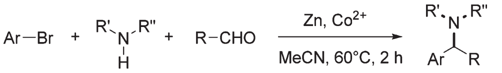
[16] The synthesis of arylzinc reagents has been described starting from aryl bromides by using zinc dust and cobalt bromide as a catalyst, see: (a) Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870. (b) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. *Tetrahedron Lett.* **2003**, *44*, 6417–6420. (c) Gosmini, C.; Amatore, M.; Claudel, S.; Périchon, J. *Synlett* **2005**, 2171–2174.

[17] The addition of Reformatsky′s reagents on preformed iminium salts has been described for the homologation of α-amino acids, see: Moumne, R.; Lavielle, S.; Philippe Karoyan, P. *J. Org. Chem.* **2006**, *71*, 3332–3334.

[18] A study indicates that α-bromo esters react with preformed imines in the presence of zinc dust under ultrasound activation to furnish mixtures of β-amino esters and β-lactams, depending on the reaction temperature, see: Ross, N. A.; MacGregor, R. R.; Bartsch, R. A. *Tetrahedron* **2004**, *60*, 2035–2041.

TABLE 3. Three-Component Reaction between an Aromatic Bromide, an Amine, and an Aldehyde[a]

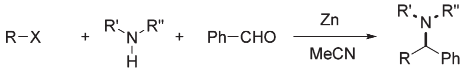


3a-f

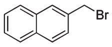
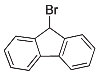
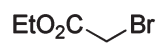
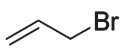
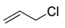
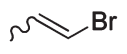
entry	Ar	amine	R		isolated yield (%)
1	Ph	pyrrolidine	Ph	**3a**	74
2	Ph	thiomorpholine	Ph	**3b**	78
3	4-anisyl	piperidine	Ph	**3c**	75
4	Ph	morpholine	thiophen-3-yl	**3d**	80
5	benzo[1,3]dioxol-5-yl	*N*-formylpiperazine	4-fluorophenyl	**3e**	70
6	3-(ethoxycarbonyl)phenyl	morpholine	thiophen-3-yl		—[b]
7	3-(trifluoromethyl)phenyl	thiomorpholine	Ph		—[b]
8	Ph	piperidine	*n*-hexyl		
9	4-isopropylphenyl	piperidine	H[c]	**3f**	82

[a] Experiments were typically conducted with 40 mL of acetonitrile, 30 mmol of the aryl bromide, 10 mmol of the aldehyde, 10 mmol of the amine, 0.66 g (3 mmol) of cobalt bromide, 0.68 g (3 mmol) of zinc bromide, and 6 g (90 mmol) of zinc dust, preactivated in the presence of TFA. [b] No reaction. [c] Paraformaldehyde was used as a formaldehyde synthetic equivalent.

TABLE 4. Three-Component Reaction between an Organic Halide, an Amine, and Benzaldehyde[a]



4a-d

Entry	Organic halide	Amine	Temp.	Time (h)		Isolated yield (%)
1		Aniline	RT	1	**4a**	56
2		Piperidine	RT	2		-
3		Aniline	RT	18	**4b**	55[b]
4		Aniline	RT	1		-
5		Aniline	60°C	18	**4c**	50[c]
6		Piperidine	60°C	1	**4d**	81[d]

[a] Experiments were conducted with 40 mL of acetonitrile, 25−30 mmol of the organic halide, 1.1 g (11 mmol) of benzaldehyde, 10 mmol of the amine, and 2−6 g (30−90 mmol) of zinc dust, preactivated in the presence of TFA. [b] Caution, vigorous reaction. [c] DMF (5 mL) and Bu_4NI (3.69 g, 10 mmol) were added before heating. [d] Cobalt bromide (0.66 g, 3 mmol) and zinc bromide (0.68 g, 3 mmol) were added to the reaction mixture before heating.

and Bu_4NI (Table 4, entry 5). An experiment was also realized when using a mixture of (*Z*)- and (*E*)-1-bromoprop-1-ene as starting compound (Table 4, entry 6). Regarding the chemical structure of this substrate, we chose to use experimental conditions analogous to those employed for the three-component coupling of aryl bromides. Under these conditions, an almost quantitative reaction is observed after 1 h at 60 °C.

It can be noted that in standard reaction conditions, alkyl halides like 1-bromoheptane do not undergo the sole three-component coupling and lead to the formation of byproducts by "dimerization" upon Würtz-like coupling or by further alkylation at the nitrogen atom of the three-component coupling product, when a primary amine is used.

In conclusion, the results reported in this study indicate that straightforward three-component reactions between various organic halides, primary or secondary amines, and aldehyde derivatives can be conducted under Barbier-like conditions. Indeed, we show that a variety of structural subunits like the diarylmethylamine, the 1,2-diarylethylamine, the α- or β-amino ester, the benzylamine, or the β-arylethylamine core can be generated with notable efficiency. Consequently, we found a promising reaction system, able to provide a wide variety of nitrogen-containing backbones in very useful reaction conditions.

Experimental Section

Representative Procedure for Benzyl Bromide. A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Zinc dust (2.0 g, 30 mmol), benzyl bromide (0.4 mL), and trifluoroacetic acid (0.2 mL) were added and the resulting solution was stirred for an additional 5 min. Then benzyl bromide (3.0 mL, 25 mmol), the amine (10 mmol), and the aldehyde (11 mmol) were introduced to the mixture, and the solution was stirred at room temperature for 1 h (exothermic reaction). The resulting solution was poured to a saturated aqueous NH_4Cl solution (150 mL), then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified over neutral alumina column with use of a solvent gradient (pentane/dichloromethane 70:30 → 0:100). Alternatively, the pure product could be obtained from the crude oil by using an acid−base workup, as detailed in ref 11b.

Representative Procedure for Aryl Bromides. A dried 100 mL round-bottomed flask was flushed with argon and charged with acetonitrile (40 mL). Cobalt bromide (0.66 g, 3 mmol), zinc bromide (0.68 g, 3 mmol), zinc dust (6 g, 92 mmol), phenyl bromide (0.32 mL, 3 mmol), and trifluoroacetic acid (0.2 mL) were added and the resulting solution was stirred for an additional 5 min. Then the aryl bromide (30 mmol), the amine (10 mmol), and the aldehyde (10 mmol) were introduced to the mixture, which was stirred at 60 °C for 2 h. The resulting solution was poured to a saturated aqueous NH_4Cl solution (150 mL), then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The crude product was purified over silica gel with a 80:20 pentane/diethyl ether mixture as eluant. Alternatively, the pure product could be obtained from the crude oil by using an acid−base workup, as detailed in ref 11b.

Supporting Information Available: Full experimental procedures, characterization data, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.