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Aromatic organozinc reagents as nucleophiles in the α-arylation of piperidine and tetrahydropyran

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Abstract—The arylation at the α-position of piperidine derivatives is achieved in good yield using aromatic organozinc reagents and either 2-methoxylated or α-cyanated piperidine. Oxygen-containing heterocycles such as 2-methoxy-tetrahydropyran reacts in a same manner to yield efficiently 2-arylated tetrahydropyran.

Piperidine derivatives constitute an important class of biologically-active compounds and numerous works were devoted to their synthesis during the last decades.[1] With respect to the predominance of 2-alkylated structures in natural products, procedures for alkylation of the 2-position have been extensively studied.[2] Fewer works have been devoted to the 2-arylation and even less to the arylation at the side chain of piperidine derivatives. Nevertheless, it was shown that phenylmagnesium chloride[3] or pyridyllithium[4] reacts with 2-activated piperidines to provide the 2-aryl-piperidine derivatives in good yields. Electron-rich substituted benzenes also react with 2-methoxylated piperidines in the presence of Lewis acids but the regioselectivity is governed by the position of the most reactive aromatic carbon.[5] By another way, palladium catalysis allows the efficient coupling of enamides[6] or α-lithio amines[7] with some aryl iodides. Examples of rearrangements[8] or cyclizations[9] leading to 2-aryl piperidines have also been described. Reductive aminations of aromatic aldehydes or ketones corresponding to arylation at the α-position of the nitrogen substituent can be realized in the presence of polymethylhydrosiloxane.[10]

To the best of our knowledge, use of aromatic organozinc reagents in the nucleophilic displacement of α-methoxylated or cyanated piperidines, which are generally considered as masked iminium equivalents, has not been previously reported. However, a large variety of functionalized aromatic organozinc derivatives are accessible and due to their broad chemical tolerance they constitute an interesting source of nucleophiles.[11] In addition, it has been shown that aliphatic organozinc compounds could act as nucleophile in Bruylants reactions.[12] Then, in a part of our work devoted to the study of the reactivity of organozinc reagents, we investigated their reactions with α-activated heterocyclic compounds and we report herein our preliminary results.

We first synthesized several electrophilic α-substituted heterocycles, which could act as valuable models (Scheme 1). Methoxylated and cyanated piperidine derivatives **1** to **3** were chosen as nitrogen-containing heterocycles. In addition and in order to test the scope of the reaction, we also synthesized an oxygenated heterocyclic compound, 2-methoxy-tetrahydropyran (**4**).

Thus, 2-phenyl-2-(piperidin-1-yl)acetonitrile (**1**) was easily synthesized starting from benzaldehyde and piperidine using a procedure described for the synthesis of (*N*,*N*-dimethylamino)phenylacetonitrile.[13] For the synthesis of 1-phenylpiperidine-2-carbonitrile (**2**), the first step was the phenylation of the nitrogen atom of piperidine.[14] The subsequent cyanation of 1-phenylpiperidine to form compound **2** was achieved electrochemically in 70% yield.[15] Other iminium equivalents, such as α-aminoethers, being widely used elsewhere in alkylation reactions, we synthesized **3** in two steps starting from piperidine, which was first converted into its N-Boc derivative using di-*tert*-butyl dicarbonate according to

Keywords: Arylation; α-Aminoether; α-Aminonitrile; Acetal; Organozinc reagent.

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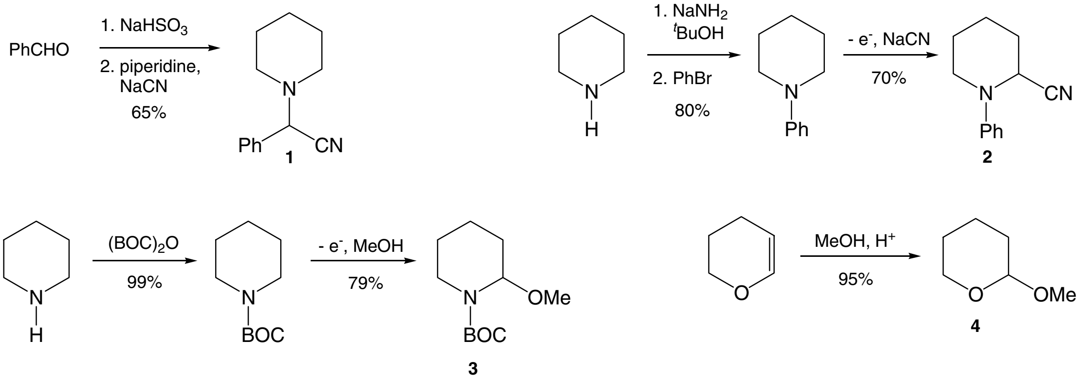


Scheme 1.

a known method.[16] *tert*-Butyl piperidine-1-carboxylate so obtained was then converted to the N-protected α-aminoether **3** in 79% yield by electrochemical methoxylation.[17]

For the synthesis of 2-methoxy-tetrahydropyran (**4**), methanol and 3,4-dihydro-2*H*-pyran were allowed to react in the presence of a catalytic amount of concentrated hydrochloric acid yielding almost quantitatively the expected compound.[18]

These masked iminium or oxonium equivalents were allowed to react with several aromatic organozinc reagents, prepared in acetonitrile according to a cobalt-catalyzed procedure developed in our laboratory.[19]

In a typical procedure, to the filtered acetonitrile solution (ca. 20 mL) of the aromatic organozinc compound (ca. 10 mmol) obtained as previously described,[19a] was added *tert*-butyl 2-methoxypiperidine-1-carboxylate (**3**) (1.08 g, 5 mmol). After a few minutes aluminum trichloride (1.4 g, ∼10 mmol) was added carefully at 0 °C and allowed to warm for 15 min at room temperature. A 10% NaOH solution (100 mL) was poured into the reaction mixture and organic materials were extracted using dichloromethane (2 × 100 mL). The organic layer was dried over potassium carbonate and concentrated to dryness. Chromatographic purification over silica gel (eluent pentane/diethyl ether mixture) afforded the coupling product[20] in good yield.

Results are reported in Table 1.

These results clearly demonstrate that either α-cyanated or 2-methoxylated piperidines can be arylated using functionalized aromatic organozinc reagents. Indeed, yields are generally good, not only with electron donating substituents connected to the phenyl ring (entries 1 and 4–8) but even with electron withdrawing groups (entries 2, 3 and 9).

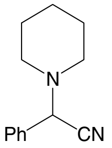
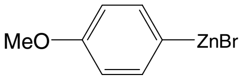
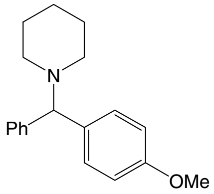
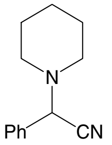
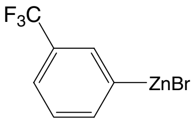
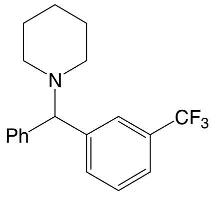
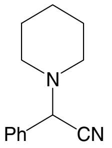
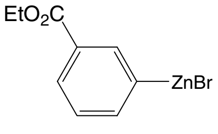
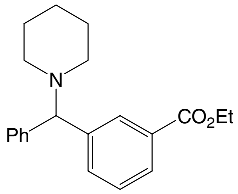
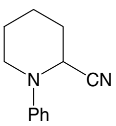
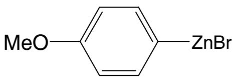
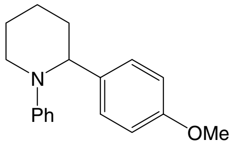
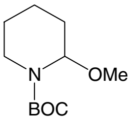
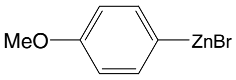
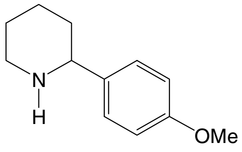
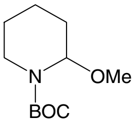
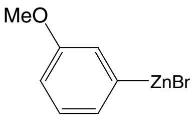
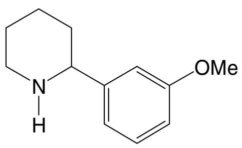
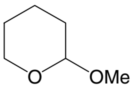
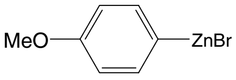
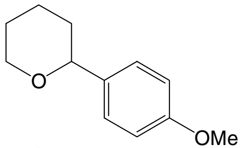
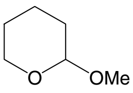
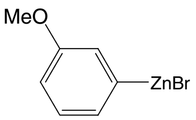
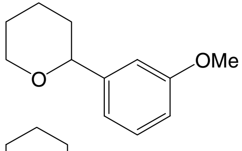
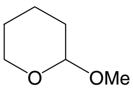
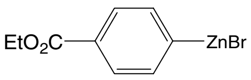
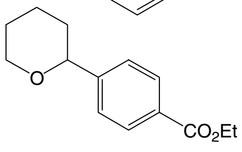
Different methods are employed in order to realize the coupling reaction, depending on the reactivity and stability of organozinc compounds. To summarize, 2-methoxylated heterocycles **3** and **4** can be displaced using organozinc reagents and aluminum trichloride (method **D**). Such a Lewis acid is required since in its absence, the reaction does not proceed fast enough and dimerization of the organozinc reagent is observed.

It can be noted that contrary to what we have experimented with methoxylated compounds, the use of an additional strong Lewis acid is not necessary when the electrophile is a cyanated compound (entries 1–4). Cobalt salts remaining from the organozinc synthesis step are still present in the solution and may act as cyanide pump.[21] Thus, starting from α-aminonitriles **1** and **2**, arylation reactions can be conducted by simply adding dropwise the organozinc compound to the heated solution of the α-aminonitrile (method **B**). This procedure, which was established considering the important degradation of electron-poor organozinc reagents in the course of time, might also be adapted to electron-rich organozinc compounds since they are at the same time more stable and reactive. Nevertheless, if one considers the case of the electron-rich organozinc reagent **5a**, a simpler one-pot reaction can be carried out. Indeed, addition of cuprous iodide raises significantly the rate of the reaction (method **A**). When the α-aminonitrile is enough reactive, the reaction proceeds very fast (ca. 15 min, entry 4) without using cuprous iodide (method **C**). Cuprous salts, which are known to enhance nucleophilicity of organozinc compounds[22] could not be used with electron-poor organozinc reagents **5b** and **5c**. Indeed, addition of cuprous iodide to these organozinc compounds gave rise to their fast dimerization into the corresponding biaryls and the formation of metallic copper indicating that a fast redox reaction occurs. In order to rationalize procedures, the addition of a strong Lewis acid like $AlCl_3$ might also be considered starting from α-aminonitriles. This could provide versatile reaction conditions starting from both methoxylated and cyanated heterocycles. Several attempts in this goal are now in progress.

Examination of reactions involving N-Boc protected piperidine **3** (entries 5 and 6) showed the simultaneous arylation and deprotection to give the expected free amines **8a** and **8d**. Such deprotections of carbamates have already been observed in the presence of $ZnBr_2$.[23]

Results presented in entries 7–9 indicate that methoxylated tetrahydropyran also react efficiently in the presence of aluminum trichloride. This leads us to hope

Table 1. Coupling of heterocyclic electrophiles with aromatic organozinc reagents

Entry	Electrophile	Organozinc	Coupling method[a]	Product	Yield (%)[b]
1	 **1**	 **5a**	**A**	 **6a**	72
2	 **1**	 **5b**	**B**	 **6b**	62
3	 **1**	 **5c**	**B**	 **6c**	65
4	 **2**	 **5a**	**C**	 **7**	80
5	 **3**	 **5a**	**D**	 **8a**	75
6	 **3**	 **5d**	**D**	 **8d**	68
7	 **4**	 **5a**	**D**	 **9a**	70
8	 **4**	 **5d**	**D**	 **9d**	63
9	 **4**	 **5e**	**D**	 **9e**	55

[a] Method **A**: CuI (0.6 g, 30% mol/mol) was added to the filtered organozinc solution (ca. 20 mL containing ca. 10 mmol reagent) and after 5 min, compound **1** (10 mmol) was added. The mixture was then stirred at rt for 3 h; Method **B**: The filtered organozinc solution (ca. 20 mL containing ca. 10 mmol reagent) was added dropwise (ca 2 h) to a boiling acetonitrile solution of the aminonitrile **1** (10 mmol); Method **C**: The filtered organozinc solution (ca. 20 mL containing ca. 10 mmol reagent) and the aminonitrile **2** (5 mmol) were allowed to react at rt for 15 min; Method **D**: To the filtered organozinc solution (ca. 20 mL containing ca. 10 mmol reagent) was added **3** or **4** (5 mmol) and after a few minutes $AlCl_3$ (~10 mmol) at 0 °C. The mixture was then allowed to react at rt for 15 min.

[b] Isolated yield.

that other oxygen-containing heterocycles can also be arylated in the same manner.

In conclusion, these results show that aromatic organozinc reagents allow the efficient nucleophilic displacement of labile substituents like methoxy or cyano groups located to the α-position of nitrogen- or oxygen-containing heterocycles for the synthesis of functionalized α-aryl piperidines or 2-aryl tetrahydropyrans.

References and notes

1. (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158; (b) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746–748; (c) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394; (d) Malassene, R.; Vanquelef, E.; Toupet, L.; Hurvois, J.-P.; Moinet, C. *Org. Biomol. Chem.* **2003**, *1*, 547–551.
2. (a) Brochieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163–2165; (b) Plehiers, M.; Hootelé, C. *Can. J. Chem.* **1996**, *74*, 2444–2453; (c) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823; (d) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490.
3. Gottlieb, L.; Meyers, A. I. *Tetrahedron Lett.* **1990**, *31*, 4723–4726.
4. Scully, F. E., Jr. *J. Org. Chem.* **1980**, *45*, 1515–1517.
5. (a) Palasz, P. D.; Utley, J. H. P.; Hardstone, J. D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807–813; (b) Malmberg, M.; Nyberg, K. *Acta Chem. Scand. Ser. B* **1981**, *35*, 411–418.
6. Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464–2470.
7. Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726–7735.
8. Shirai, N.; Sumiya, F.; Sato, Y.; Hori, M. *J. Org. Chem.* **1989**, *54*, 836–840.
9. Boivin, J.; Pothier, J.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 3701–3704.
10. Chandrasekhar, S.; Raji Reddy, Ch.; Ahmed, M. *Synlett* **2000**, 1655–1657.
11. (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (b) Knochel, P.; Jones, P. In *Organozinc Reagent, A Practical Approach*; Harwood, L. M., Moody, C. J., Eds.; Oxford University Press: Oxford, 1999.
12. Bernardi, L.; Bonini, B. F.; Capito, E.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778–1782.
13. *Organic Syntheses, Collective*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Vol. 5, pp 437–439.
14. Caubère, P.; Derozier, N. *Bull. Soc. Chim. Fr.* **1969**, 1737–1745.
15. We thank J.-P. Hurvois, UMR 6509, University of Rennes 1 for providing us α-aminonitrile **2**. For a description of a standard electrochemical cyanation procedure see Ref. 1d.
16. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117.
17. Torii, S.; Inokuchi, T.; Akahosi, F.; Kubota, M. *Synthesis* **1987**, 242–245.
18. Woods, G. F.; Kramer, D. N. *J. Am. Chem. Soc.* **1947**, *69*, 2246.
19. (a) Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870; (b) Fillon, H.; Gosmini, C.; Périchon, J. Patent Application in France, 4 July 2001, no. 01/08880; (c) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. *Tetrahedron Lett.* **2003**, *44*, 6417–6420.
20. Coupling products were characterized using ^{1}H NMR (200 or 300 MHz), ^{13}C NMR (50 or 75 MHz), HRMS and in some cases FT IR.
21. pK_ds of cyanide complexes of cobalt(II) are very high.
22. Le Gall, E.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron* **2001**, *57*, 1923–1927, and references cited herein.
23. Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C. G. *Synth. Commun.* **1989**, *19*, 3139–3142.