

0040-4039(94)02436-7

Ortho-metalated Aromatic Tertiary Amides: New Synthetic Applications

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Abstract: Ortho-lithio-cuprate species derived from aromatic tertiary amides exhibited a significantly larger field of application than the lithio precursors.

Since its disclosure by Gilman and Wittig fifty-five years ago, the *ortho*-metalation of "activated" aromatic compounds has been widely developed and now constitutes one of the most potent methodologies for the regioselective elaboration of polysubstituted aromatics.² Among the *ortho*-director groups which have been proposed, the most useful proved to be unquestionably the tertiary amide, originally introduced by Beak in 1982 (Equation 1).³ Syntheses of a great variety of complex aromatic derivatives, based on the use of such an activating group, have thus been achieved.^{2b}



In this paper, we show that the *ortho*-lithic cuprate complexes derived from the aromatic tertiary amides exhibit a more versatile reactivity than the parent lithic compounds, thereby extending notably the synthetic scope of such functionalized organometallics.

In connection with our synthetic efforts in the taxane series, we recently planed the construction of contiguously trisubstituted aromatic systems. Such derivatives would be elaborated through the *ortho*-lithiation of adequatly substituted tertiary amides. In this respect, the allylation of 2-methoxy-N,N-diethylbenzamide 1 was first investigated. However, sequential treatment of 1 with *sec*-BuLi-TMEDA complex (-78 °C, THF, 25 min) and allyl bromide (-78 °C \rightarrow 20 °C) led to bromide 2⁴ with a 74% yield, instead of the allylated derivative (Table 1, entry 1).³ A similar result was obtained with allyl iodide, the iodo derivative 3⁵ being isolated with a 86% yield (Table 1, entry 2). A facile metal/halogen exchange was also observed in the reaction of the *ortho*-lithio derivative of amide 4 with allyl bromide (Table 1, entry 3; however in the present case the bromide 5⁶ was accompanied by a substantial amount of the allylated derivated 6) and with benzyl bromide (Table 1, entry 4; note that a nearly quantitative amount of bibenzyl 8⁷, the result of the trapping of benzyllithium -formed by metal/halogen exchange- with the excess of benzyl bromide, was isolated in that case).

The Li/halogen exchange observed in the preceding reactions is clearly facilitated by the ability to form stabilized (allylic or benzylic) anionic species. Indeed, reaction of the lithio derivative of 4 with ethyl iodide furnished in contrast the ethylated derivative 9 with a 62% yield (Table 1, entry 5).

Entry	Starting aromatic amide	sec-BuLi- TMEDA complex mol ratio /1 or 4	Alkyl halide mol ratio /1 or 4	Products (yield)
1		1.1	Br (2.1)	MeOBr 2 (74%)
2	1	1.1	(2.1)	MeOI 3 (86%)
3		1.5	Br (2.5)	$\begin{array}{c} 4 \\ (23\%) \end{array}^{+} \bigcirc ^{NEt_2} \\ 5 (40\%) \end{array}^{+} \bigcirc ^{NEt_2} \\ 5 (40\%) \\ 6 (12\%) \end{array}$
4	4	2.0	Br Ph (2.6)	$ \begin{array}{c} $
5	4	1.5	(2.5)	O NEt₂

Table 1. Reaction of lithiated aromatic amides with alkyl halides

Quite surprisingly, examination of the condensation of *ortho*-lithiated aromatic tertiary amides with allyl bromide through the literature revealed inconsistent precedents. Thus, although reported as leading to *ortho*-bromoamides by Beak in 1982,³ this reaction was notified ten years later by Snieckus as furnishing " spurious results".⁸ However, in our hands, this reaction proved to be perfectly reproductive, giving fair to good yields of *ortho*-bromobenzamides (*vide supra*).

In view of such results, we decided to modify the reactivity of the *ortho*-lithiated amide species, by transmetalation with CuI.^{9,10} To our delight, the lithio-cuprate complexes¹¹ thus formed exhibited a significantly larger field of application than the lithio precursors. Thus the condensation with allyl bromide or benzyl bromide now proceeded straightforwardly, giving the desired alkylated derivatives 10^{12} , 6^{13} and 7^{14} in good yields (Table 2, entries 1,2 and 3). The reactivity of several other electrophiles, known to fail to condense with *ortho*-lithiated aromatic amides 8,9a was also explored. When methyl bromoacetate led with a very low yield to the bis-alkylated compound 11^{15} (Table 2, entry 4), *o*-anisoyl chloride furnished the expected ketone 12^{16} with a 92% yield (Table 2, entry 5). Very interestingly these cuprate reagents added smoothly to cyclohexenone in the presence of TMSCl, giving acceptable yields of the conjugate adduct 13 (Table 2, entries 6)

Entry	Starting aromatic amide	sec-BuLi- TMEDA complex mol ratio /1 or 4	CuI-Me ₂ S complex mol ratio /1 or 4	Electrophile mol ratio /1 or 4	Products (yield, see footnotes)
1		1.1	2.0	Br (2.1)	MeO 10 (78%)
2	0 NEt ₂	2.0	2.0	Br (2.5)	0 NEt2 6 (82%)
3a	4	2.0	2.0	BrPh (2.6)	0 NEt ₂ Ph 7 (74%)
4b	4	3.0	1.4	Bracoome	О NEt2 СООМе СООМе 11 (10%)
5	4	3.0	1.4		о NEt2 ОМе О 12 (92%)
6¢	4	2.0	2.0	(2.0) TMSCI (2.1)	Et ₂ N OTMS 13 (25%)
7d,e	4	3.0	1.4	(3.0) TMSCI (3.3)	13 (45%)

 Table 2. Reaction of ortho-lithio cuprate complexes of aromatic tertiary amides with electrophiles

a: 14% of 14¹⁷ and 11% of starting material 4 were also obtained. b: 15% of 4, 11% of 14 and 18% of 15¹⁸ were also isolated. c: 49% of 4 and 20% of 14 were also obtained; d: 26% of 4 and 25% of 14 were also isolated. e: mild acidic hydrolysis of silyl enol ether derivative 13 led quantitatively to 16¹⁹.



and 7). It should be noted that significant amounts of by-products 14 and 15 (see footnotes, Table 2) were frequently formed in these condensations, probably due to the thermal instability of the lithio-cuprate species.

Work is pursued in our laboratory to extend the synthetic application of these organometallics.

Acknowledgments. This work has been supported in part by a Grant from the European Communities (The Rational Design of New Organic Molecules and Synthetic Methods, Contract Nr ERBCHRXCT 930141). We thank also Dr A. Talab (Société MERAM, Melun, France) for GC-MS analyses.

References and Notes

- 1. EC Postdoctoral Fellow, on leave from the Universitat Autonoma de Barcelona (Spain).
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 Beak, P.; Brown, R.A. J. Org. Chem., 1982, 47, 34-46.
- 4. 2: mp 65-66 °C (Et₂O/hexane); IR (KBr, cm⁻¹) 1633; ¹H NMR (200 MHz, CDCl₃) δ 7.17 (m, 2H), 6.88 (m, 1H), 3.83 (dq, J = 7.2, 14.1 Hz, 1H), 3.82 (s, 3H), 3.41 (dq, J = 7.2, 14.1 Hz, 1H), 3.15 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.08 (t, J = 7.2 Hz, 3H); MS (CI, NH₃) 286/288 (M+H⁺).
- 5. 3: mp 46-48 °C (Et₂O/hexane); IR (KBr, cm⁻¹) 1627; ¹H NMR (200 MHz, CDCl₃) δ 7.31 (dd, J = 7.7, 0.9 Hz, 1H), 6.93 (dd, J = 8.3, 7.7 Hz, 1H), 6.81 (dd, J = 8.3, 0.8 Hz, 1H), 3.78 (dq, J = 7.2, 14.1 Hz, 1H), 3.71 (s, 3H), 3.26 (dq, J = 7.2, 14.1 Hz, 1H), 3.05 (q, J = 7.2 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H); MS (CI, NH₃) 334 (M+H⁺).
- 5: mp 47-48 °C (Et₂O/hexane); IR (KBr, cm⁻¹) 1634; ¹H NMR (200 MHz, CDCl₃) δ 7.33 (d, J = 7.9, 1H), 7.06 (m, 3H), 3.62 (dq, J = 7.2, 14.1 Hz, 1H), 3.12 (dq, J = 7.2, 14.1 Hz, 1H), 2.92 (dq, J = 7.2, 2.1 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H); MS (CI, NH₃) 256/258 (M+H⁺).
- 7. 8: mp 49-51 °C (MeOH); ¹H NMR (200 MHz, CDCl₃) δ 7.12 (m, 10H), 2.85 (s, 4H).
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- For examples of transmetalation of o-lithio benzamides with (a) MgBr2: Sibi, M.P.; Miah, M.A.J.; Snieckus, V. J. Org. Chem., 1984, 49, 737-742 (in that case, the condensation with allyl bromide led to the allylated derivatives with good yields); (b) MgBr2 and NiCl2(PPh3)2: Sibi, M.P.; Dankwardt, J.W.; Snieckus, V. J. Org. Chem., 1986, 51, 271-273.
- 10. Transmetalation of o-lithio aryloxazolines with CuBr: Ellefson, C.R. J. Org. Chem., 1979, 44, 1533-1536.
- 11. For a review, see: Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *Tetrahedron*, **1984**, 40, 5005-5038. The lithio-cuprate species were formed at -78 °C by exchange with CuI-Me₂S complex in Et₂O solution (30 min). The electrophiles were then added at this temperature.
- 12. **10**: IR (neat, cm⁻¹) 1632; ¹H NMR (400 MHz, CDCl₃) δ 7.24 (dd, J = 8.2, 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 5.94 (m, 1H), 5.04 (m, 2H), 3.79 (s, 3H), 3.79 (dq, J = 7.2, 14.1 Hz, 1H), 3.25 (m, 3H), 3.09 (dq, J = 7.2, 2.1 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H).
- 13. **6**: IR (neat, cm⁻¹) 1634; ¹H NMR (200 MHz, CDCl₃) δ 7.21 (m, 4H), 5.89 (m, 1H), 5.04 (m, 2H), 3,68 (m, 1H), 3.34 (d, J = 6.7 Hz, 2H), 3.32 (m, 1H), 2.94 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H).
- 14. 7: IR (neat, cm⁻¹) 1633; ¹H NMR (200 MHz, CDCl₃) δ 7.15 (m, 9H), 3,94 (m, 2H), 3.54 (m, 1H), 3.22 (m, 1H), 2.73 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H).
- 15. **11**: IR (KBr, cm⁻¹) 1743,1627; ¹H NMR (400MHz, CDCl₃) δ 7.34 (m, 4H), 4.11 (m, 1H), 3.73 (m, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.41 (m, 1H), 3.20 (m, 2H), 3.04 (m, 1H), 2.75 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 7.2 Hz, 3H); MS (CI, NH₃) 322 (M+H⁺).
- 16. **12**: IR (KBr, cm⁻¹) 1667,1633; ¹H NMR (200MHz, CDCl₃) δ 7.39 (m, 6H), 6.92 (m, 2H), 3.65 (s, 3H), 3.45 (q, J = 7.2 Hz, 2H), 3.14 (q, J = 7.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H).
- 17. **14**: IR (KBr, cm⁻¹) 1631;¹H NMR (200 MHz, CDCl₃) δ 7.33 (m, 8H), 3.78 (m, 2H), 3.38 (m, 2H), 3.10 (m, 4H), 1.04 (t, J = 7.2 Hz, 6H), 0.98 (t, J = 7.2 Hz, 6H); MS (CI, NH₃) 353 (M+H⁺).
- 18. **15**: IR (KBr, cm⁻¹) 1633; ¹H NMR (90 MHz, CDCl₃) δ 7.25 (m, 4H), 3.75 (m, 1H), 3.4 (m, 1H), 3.1 (q, J = 7.2 Hz, 2H), 2.6 (m, 1H), 1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 7.2 Hz, 3H), 1.0 (t, J = 7.2 Hz, 3H), 0.80 (t, J = 7.2 Hz, 3H); MS (CI, NH₃) 234 (M+H⁺).
- 19. **16**: IR (neat, cm⁻¹) 1713,1628; ¹H NMR (200MHz, CDCl₃) δ 7.24 (m, 4H), 3.69 (m, 1H), 3.26 (m, 1H), 3.02 (q, J = 7.2 Hz, 2H), 2.91 (m, 1H), 2.73-2.00 (m, 6H), 1.75 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H).