to an aqueous solution containing 5 molar equiv of NaOH and 2 molar equiv of $K_3Fe(CN)_6$ resulted in vigorous gas evolution with concomitant formation of the acetylenes **6a–e**.[4] As can be seen from Table I, this reaction is synthetically useful when the vinyl radical bears an aryl substituent (R_1 = Ph). The diminished yields of acetylenes **6c–e** (R_1 = alkyl) probably reflects a decreased stability (and, hence, lifetime) for the corresponding radicals **4c–e**.

The synthetic potential of this procedure is exemplified by the synthesis of junipal (**14**),[5] an odiferous constituent of the wood-rotting fungus *Daedalea juniperina* (Scheme II) in 24% overall yield from 2-propionylthiophene (**9**).[6] The key step of the synthesis, the oxidative decomposition of the bromopyrazolinone **12**, proceeded in 66% yield to 2-(1-propynyl)thiophene (**13**) which was then converted to junipal[7] by standard procedures[5b] in 66% yield.

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(4) In the absence of the $K_3Fe(CN)_6$, the olefinic acids of **8** are produced in ≥70% yield, whereas the yield of acids is ≤10% when the oxidizing agent is present.

(5) Previous syntheses: K. F. Schulte and N. Jantos, *Arch. Pharm.*, **292**, 536 (1959); L. Skattebol, *Acta Chem. Scand.*, **13**, 1460 (1959); K. E. Schulte, J. Reisch, and L. Hörner, *Chem. Ber.*, **95**, 1943 (1962); F. Bohlmann and E. Bresinsky, *ibid.*, **106**, 107 (1967); R. F. Curtis and G. T. Phillips, *J. Chem. Soc. C*, 578 (1967).

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(7) Mp 81–82 °C (lit.[5b] mp 81–82 °C); ir (CCl_4) 2840, 2810, 2740, 2240, 1670, 1450, 1435, 1215, 1045, and 670 cm^{-1}; NMR (CCl_4) δ 9.7 (s, 1 H), 7.48 (d, 1 H, J = 4 Hz), 7.05 (d, 1 H, J = 4 Hz), 2.1 (s, 3 H).

P. J. Kocienski,* J. M. Ansell, B. E. Norcross
Department of Chemistry
State University of New York at Binghamton
Binghamton, New York 13901

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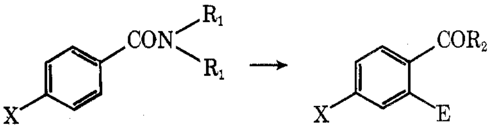
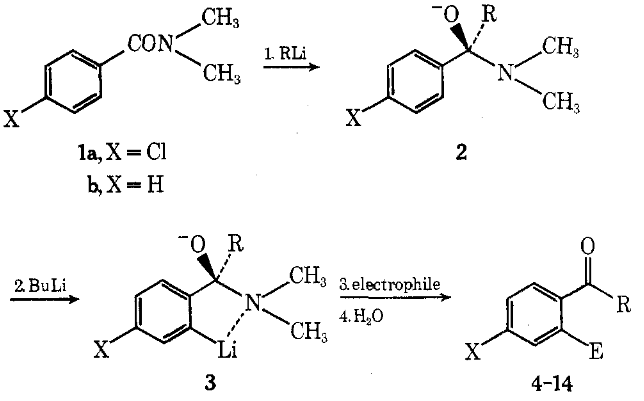
Ortho-Lithiation. A Regiospecific Route to Ortho-Substituted Aryl Ketones

Summary: A method is described to convert *N,N*-dimethylbenzamides directly into ortho-substituted aryl ketones via addition of RLi, followed by ortho-lithiation and reaction with an electrophile.

Sir: To date a direct and general synthesis of ortho-substituted aryl ketones from readily available starting materials has not been reported. The potential route via nucleophilic substitution of the appropriate diazonium salts is limited by the availability of the corresponding anilines. Moreover, such reactions may take a different course, such as the internal cyclization to cinnolines.[1] Alternatively, direct electrophilic substitution of aryl ketones is a formidable problem at best. We here wish to report a practical approach to this problem based on heteroatom directed lithiation. The overall transformation, which is carried out as a one-pot reaction, starts with a tertiary benzamide and leads to the desired ortho-functionalized aryl ketones.

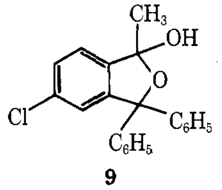


Since dialkylbenzylamines can be lithiated in the ortho position,[2] it was assumed that the tertiary amine in the tetrahedral intermediate **2**, generated by the addition of RLi to a tertiary arylcarboxamide, should also serve as an ortho-directing ligand for a subsequent lithiation. The reaction of



intermediate **3** with an electrophile followed by aqueous workup then ought to produce the desired ortho-substituted aryl ketone. Tetrahedral intermediates of type **2** have provided regiospecificity in the α-metalation of thiophenes[3–5] and furans,[6] as reported by two separate groups. This superficially can serve as precedent for our postulate. However, since it has been well established that the α positions of five-membered heterocycles are generally deprotonated much more readily than benzenoid systems,[7] it was by no means certain that the desired metalation could be realized. It was, therefore, not only of theoretical, but, as indicated at the outset, of considerable practical interest to test the feasibility of this concept.

The reaction works remarkably well, and, although the isolated yields are not spectacular,[8] they are quite respectable considering the number of operations actually carried out. As indicated in Table I, the method is quite general in terms of the nature of both RLi (step 1) and the electrophile (step 3). It should be pointed out that, in cases where the newly introduced ortho substituent E can serve as an internal nucleophile, cyclic products are isolated exclusively as documented by entries **9**, **12**,[9] and **13**. Another item deserving special attention is the high degree of regioselectivity attained in the preparation of **7**. Whereas in principle deprotonation could occur in either of the two phenyl rings (R = C_6H_5) during the metalation step (2), the rate-enhancing effect of



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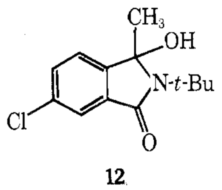

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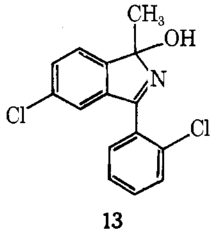

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Table I[a]

Benzamide	RLi[b]	Conditions for step 2[c]	Electrophile	Product	E	Mp or bp, °C	Yield,[d] %	
							Isold	GC, NMR
1a	CH_3Li	25/16	$(CH_3S)_2$	**4**	SCH_3	62	45	
1a	EtLi	0/20	$(CH_3S)_2$	**5**	SCH_3	67	46.5	70[e]
1a	BuLi	0/16	$(CH_3S)_2$	**6**	SCH_3	52	55.5	
1a	C_6H_5Li	25/16	$(CH_3S)_2$	**7**	SCH_3	49	53	55[f]
1b	CH_3Li	25/16	$(CH_3S)_2$	**8**	SCH_3			60[e]
1a	CH_3Li	25/16	$(C_6H_5)_2CO$	**9**	$[(C_6H_5)_2COH]$[g]	132	46.8	
1a	CH_3Li	25/16	CH_3I	**10**	CH_3	150 (0.1 mm)		81[f]
1a	CH_3Li	25/16	DMF	**11**	CHO	165 (0.7 mm)	56	
1a	CH_3Li	25/16	*t*-BuNCO	**12**	(CONH-*t*-Bu)[g]	136	41	
1a	CH_3Li	0/8	*o*-ClC_6H_4CN	**13**	(*o*-$ClC_6H_4C{=}NH$)[g]	192	53	
1a	C_6H_5Li	25/16	DMF	**14**	CHO	50	37	55[f]

[a] All compounds reported show satisfactory analytical data. [b] RLi was added to a THF solution of **1** at −70 °C, although the low temperature does not appear to be critical. [c] Temperature in °C/hour. The addition of *n*-BuLi was carried out at ice-bath temperature. [d] Yields were generally not optimized. [e] GC. [f] NMR. [g] These compounds exist as cyclic tautomers. Compound **9** is a 71:29 equilibrium mixture of cyclic and open form in $CDCl_3$.

the 4-chloro substituent provides the observed regioselectivity.

In a typical example, a solution of 10 g of **1a** (55 mmol) in 100 ml of THF was cooled to −78 °C. One hour after the addition of an ethereal solution of CH_3Li (31.2 ml, 2.0 M, 59 mmol), 36.8 ml (59 mmol) of a 1.6 M *n*-BuLi solution in hexane were added. The mixture was then allowed to stir at room temperature for 16 h. Then a solution of 4.4 g (59 mmol) of DMF in 20 ml of THF was added at ice-bath temperature. After stirring for 1 h at ambient temperature, the reaction was quenched with 3 N HCl and the product extracted into ether. After drying (Na_2SO_4) and evaporation of the organic layer, the oily residue (6.5 g) was distilled to give 5.6 g of 5-chloro-2-acetylbenzaldehyde (**11**), bp 165 °C (0.7 mmHg).

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Supplementary Material Available. Full experimental details and analytical data on compounds **4–14** (6 pages). Ordering information is given on any current masthead page.

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(8) The major additional products in these reactions are, not unexpectedly, the corresponding phenones resulting from quenching either **3** or more likely the nonmetalated **2** in the workup. After the submission of the manuscript it was observed that addition of a larger excess of *n*-BuLi gave a high yield of the ortho-metalated species **3**, indicating partial consumption of the metalating agent by the solvent (THF) [cf. R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972).
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Lester Barsky, Heinz W. Gschwend*
Joe McKenna, Herman R. Rodriguez
Research Department, Pharmaceuticals Division
CIBA-GEIGY Corporation, Summit, New Jersey 07901

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