

Carbolithiation of aromatic rings: cyclohexadienes from *N*-aroyl-2,2,6,6-tetramethylpiperidines

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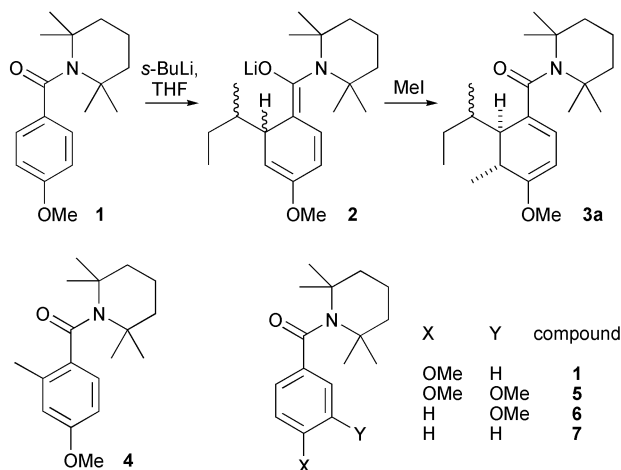
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Benzamides whose nitrogen atom is part of a 2,2,6,6-tetramethylpiperidine ring are dearomatised by alkyllithiums, which attack them regioselectively to yield, after electrophilic quench, substituted cyclohexadienes.

Dearomatisation of aromatic rings allows chemists to superimpose stereoselective reactions upon the regiochemical control available with aromatic substitution chemistry, both classical and metallation-directed.¹ Methods for partial dearomatisation are particularly useful for making substituted cyclohexanes and cyclohexenes since they can give synthetic intermediates containing a valuable combination of reactive unsaturated functional groups. Other than Birch reduction,^{2–4} which allows only electrophilic functionalisation of the ring, rapid dearomatisation elaboration of benzenoid rings is best achieved by nucleophilic addition to an electron deficient arene lacking other points of electrophilic reactivity.⁵

The need for an electron-withdrawing group which is not itself electrophilic is the greatest limitation to new intermolecular⁶ dearomatisation addition reactions. The most common solution to this problem is to complex the ring with a metal, usually chromium, which permits ring addition with stereo- and regiocontrol.⁷ An alternative strategy is to employ a carbonyl-substituted starting material but to block reactivity at the carbonyl group itself, for example with hindered Lewis acids.⁸ In this communication, we show that amides of 2,2,6,6-tetramethylpiperidine (TMP) perform in a similar role, allowing the addition of an organolithium and an electrophile across one of the double bonds of an arene in the manner of a carbolithiation reaction.⁹

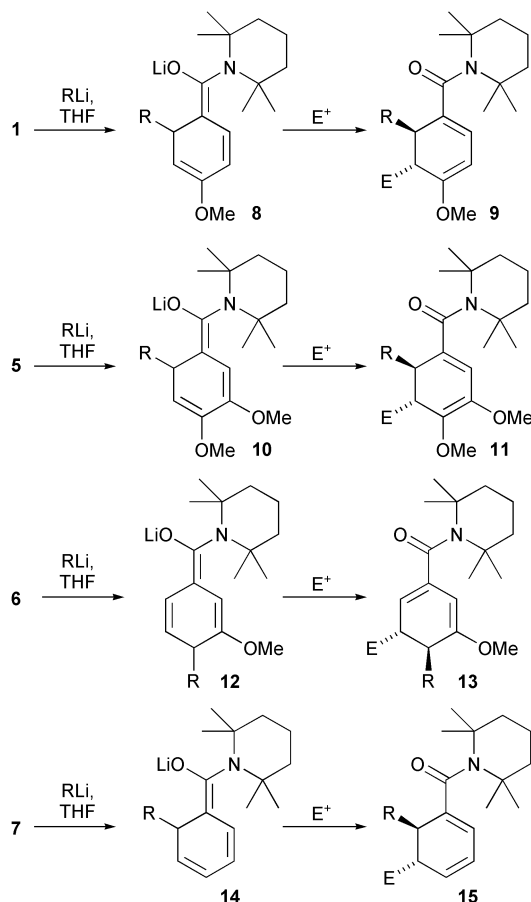
Treatment of **1** with *s*-BuLi in THF at -78 or 0 °C and then methyl iodide in an attempted ortholithiation reaction gave, instead of the expected¹⁰ **4**, a good yield of the dearomatised compound **3a** as a mixture of diastereoisomers at the stereogenic centre in the *sec*-butyl group (Scheme 1).[†] Nucleophilic addition to the aromatic ring takes place in preference to deprotonation, forming an extended enolate **2** which alkylates at its terminus.

Scheme 1 TMP amides and *sec*-butyllithium.

To evaluate the scope of the nucleophilic dearomatisation, we treated a small range of TMP amides **1** and **5–7**† with organolithiums RLi (*n*-BuLi, *s*-BuLi, and MeLi), quenching with a range of electrophiles E⁺ (Scheme 2). Table 1 shows the results of this study.

The enolate produced by addition of *s*-BuLi to **1** reacted with a range of electrophiles in moderate to good yield (entries 1–5). Except for protonation, which gave a mixture of regioisomers, the extended enolates always reacted at their termini, yielding the 2,3-disubstituted cyclohexanecarboxamides **3**. The electrophilic quench was stereoselective, giving only the *trans* diastereoisomer. *n*-BuLi and MeLi also added to **1**, and although yields were lower than with *s*-BuLi, single diastereoisomers of products **3f** and **3g** were obtained in each case (entries 6 and 7). The remainder of the material was largely made up of unreacted starting amide.

The *p*-methoxy substituent assists but is not necessary for the dearomatisation addition. *N*-Benzoyl-2,2,6,6-tetramethylpiperidine **7**, for example, reacts with *s*-BuLi to give a comparable enolate **14** whose quench with methyl iodide yields **15** as a mixture of diastereoisomers (entry 11).

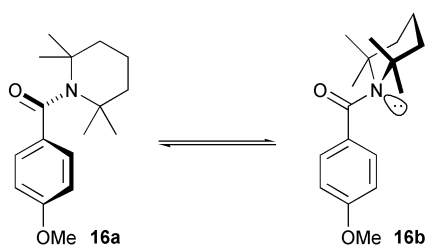


Scheme 2 Carbolithiation of TMP amides.

Table 1 Dearomatising carbolithiation–quench of TMP amides

Entry	Starting material	R	E ⁺	Product	Yield (%)
1	1	<i>s</i> -Bu	MeI	9a (= 3a)	71 ^a
2			BnBr	9b	61 ^a
3			EtI	9c	51 ^a
4			(CH ₂) ₃ C=O	9d	32 ^a
5			NH ₄ Cl	9e	76 ^{ab}
6		<i>n</i> -BuLi	MeI	9f	40
7		MeLi	MeI	9g	22
8	5	<i>s</i> -Bu	MeI	11a	12
9	6	<i>s</i> -Bu	MeI	13a	23
10			NH ₄ Cl	13b	15 ^c
11	7	<i>s</i> -Bu	MeI	15a	55

^a 3:1 Mixture of diastereoisomers at Et(Me)CH. ^b Mixture of γ and ϵ -protonated regioisomers. ^c α -Protonated regioisomer.

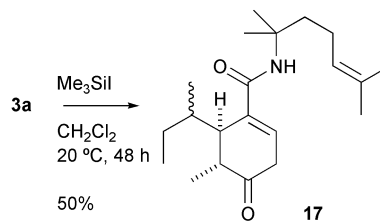
**Scheme 3** Conformation and reactivity.

Other substituted benzamides react less efficiently. The 3,4-dimethoxybenzamide **5** reacts in a manner analogous to **1** and **7** but only very slowly—the reaction in entry 8 returns mainly starting amide. The *m*-methoxy substituted compound **6** by contrast undergoes addition of *s*-BuLi at the *para* position, and quenching with MeI or protonation generates diastereoisomers of **13a** and **13b**.

Amides of TMP have unusual structural features, which display themselves spectroscopically, and which may shed light on this unusual reactivity.¹¹ Most significantly, the barrier to C–N rotation in the amides is particularly low: 28 kJ mol⁻¹ for **7**¹¹ compared with *ca.* 65 kJ mol⁻¹ for *N,N*-dimethylbenzamide.¹² This must be due to steric encumbrance of the normal planar amide structure, and we propose that while **1** probably adopts conformation **16a**, with the ring twisted out of the amide plane, as its ground state, a de-conjugated conformation approximating to **16b** is relatively easily accessible (Scheme 3). In conformation **16b**, Ar–CO conjugation activates the ring towards nucleophilic attack while the four methyl groups shield the carbonyl from the incoming nucleophilic reagent, and we propose that dearomatisation arises by attack on **16b**.

The TMP feature of the amide is relatively sensitive to cleavage under acid conditions. For example, treatment of **3a** (= **9a**) with iodotrimethylsilane in the absence of light cleaved both the enol ether and the TMP ring, yielding the secondary amide **17** in 50% yield (Scheme 4).

Treatment of hindered amides with strong bases is well established as a method for the synthesis of aromatic compounds by ortholithiation.¹⁰ This reaction appears to place some limits of the types of amides which may be successfully ortholithiated, but it also opens up new prospects for the use of

**Scheme 4** Deprotecting the amide.

aromatic rings as precursors of substituted cyclohexane derivatives without recourse to transition metal chemistry.

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Notes and references

† *Typical procedure:* *sec*-Butyllithium (1.3 M in hexane, 0.68 ml, 1.2 equiv.) was slowly added to a stirred solution of the amide **1** (0.20 g, 0.74 mmol) in dry THF (7 ml) at 0 °C under nitrogen. After 1 h, iodomethane (0.14 ml, 3 equiv.) was added and the mixture was allowed to warm to room temperature. After a further 45 min, a saturated solution of ammonium chloride (15 ml) was added and the mixture was extracted with ethyl acetate (2 × 20 ml). The combined organic phases were washed with brine (2 × 20 ml) and dried over magnesium sulfate. Concentration under reduced pressure yielded the crude product as yellow oil. Purification by flash chromatography (1:14 EtOAc–petroleum ether (bp 40–60)) afforded the *dearomatised product 3a* (0.19 g, 71%) as a mixture of diastereoisomers (3:1), plus starting material **1** (12 mg, 6%). Data for major diastereoisomer: δ_{H} (300 MHz; CDCl₃): 7.40 (1 H, d, *J* 6.6), 4.97 (1 H, d, *J* 6.6), 3.66 (3H, s), 2.69 (1 H, d, *J* 2.7), 2.28 (1 H, q, *J* 7.2), 1.72 (3H, m), 1.52 (3 H, td, *J* 6.0, 2.4), 1.28–1.20 (12 H, m), 1.06–0.92 (6 H, m) and 0.72 (3 H, d, *J* 6.9); ν_{max} 1625 cm⁻¹ (C=O); MS: found, *M* + *H*⁺, *m/z* 348.2903. C₂₃H₃₈NO₂ requires *M*, 348.2902.

‡ The amides were formed by heating to reflux the appropriate acyl chloride with the sodium salt of 2,2,6,6-tetramethylpiperidine in toluene for 24 h.

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