Directed metalation groups (DMGs) are sometimes compromised by the inability to convert them to different functionalities under mild conditions in post-directed ortho metalation (DoM) steps.\(^1\) The advent of N-cumyl modified carboxamide, sulfonamide and O-carbamate DMGs,\(^2\) whose primary advantages over analogous N-\(t\)-Bu\(^3\) and other N-alkyl systems rest in fast and/or mild hydrolysis post-DoM, has opened new possibilities for the manipulation of substituted aromatics (Scheme 1). Starting materials are easily prepared by treating the appropriate benzoyl or sulfonyl chlorides with cumyl amine\(^4\) for access to benzamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary N-alkyl-N-cumyl amine\(^5\) for access to benzenamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary N-alkyl-N-cumyl amine\(^6\) for O-carbamates.

This Spotlight reviews several applications of N-cumyl-substituted functional groups in organic synthesis since the preliminary results of 1999.\(^2\)

**Abstracts**

Ortho-substituted N-cumylbenzamides and aryl O-carbamates may be easily decumylated\(^2\) under a number of conditions.\(^2\) Treatment of secondary N-cumylbenzamides with a Lewis acid (BF\(_3\)OEt\(_2\)/CH\(_2\)Cl\(_2\)/r.t.) gives primary amides in good yields, while application of Charette’s conditions\(^6\) (Tf\(_2\)O/pyridine/CH\(_2\)Cl\(_2\)/–40 °C) affords benzonitriles in one pot. Similarly, O-carbamates undergo rapid decumylation (TFA/r.t./6–10 min) to yield benzoxazines or secondary carbamates; the latter may be easily hydrolyzed to phenols (10% NaOH/EtOH/r.t.).
Metalation of N-cumyl phthalimidine (2.2 equiv s-BuLi/TMEDA/THF/78 °C) followed by electrophile quench gives, after oxidation (PDC/DMF/r.t.) access to 3-substituted phthalimides that can be decumylated (TFA/50 °C) in high yield. The method has been extended to TMS-protected sulfamides derived from N-cumylbenzenesulfonamide, to afford 7-substituted saccharins after simple desilylation (K₂CO₃/MeOH), oxidation (PDC/DMF/r.t.) and decumylation (CF₃CH₂OH/reflux/90 min). Alternatively, decumylation of 7-substituted TMS-protected sulfamides (CF₃CH₂OH/reflux) provide direct access to 7-substituted benzisothiazole-1,1-dioxides.

Weinreb has shown that N-cumyl-N-(α-methoxy)benzylbenzamides may be used to generate N-acylilines (BF₃·OEt₂/CH₂Cl₂/r.t./18–21 h) which can be trapped with allyltrimethylsilane, with concomitant loss of the N-cumyl group, to afford N-homoallylic secondary benzamides.

Clayden has used N-cumyl-N-benzylbenzamides to induce de- aromatizing cyclization reactions, initiated by benzylic anion formation (2 equiv t-BuLi/12 equiv HMPA/THF/40 °C), to provide enone products after acidic workup. The use of cumyl as the N-protecting group in such systems was a key aspect to the successful synthesis of (±)-kainic acid, since the corresponding t-Bu analogue failed to dealkylate under identical conditions (TFA/reflux/6 h).

Enantioselective applications are also possible. N-Cumyl-N-ethylferrocene carboxamide stERICALLY mimics N,N-diisopropylferrocene carboxamide in (−)-sparteine-mediated metalation to provide 2-substituted ferrocenes in good yield. Unlike the original N,N-diisopropyl systems, the products are open to flexible manipulation by virtue of decumylation under very mild conditions (CF₃CH₂OH/reflux/5–12 h) to give, usually quantitatively, enantiomerically enriched secondary ferrocene carboxamides for further transformations. For example, N-allylation of N-ethyl-2-vinylferrocene carboxamide followed by olefin metathesis with Grubbs’ catalyst gives, after hydrogenation, a planar chiral ferrocenyl azepinone. Subsequent metalation and electrophile quench (Ph₂PCl) affords structurally novel phosphine ligands.

References


(3) More forcing conditions are required to dealkylate N-t-Bu benzamides; see: Reitz, D. B.; Massey, S. M. J. Org. Chem. 1990, 55, 1375.

(4) (a) Cumyl amine can be prepared from cumyl alcohol by a modification of the procedure of: Balderman, D.; Kalir, A. Synthesis 1978, 24. The azide is reduced with LiAlH₄, (Et₂O/0 °C → r.t. → reflux) or H₂ (Lindlar’s catalyst/EtOH) instead of Raney nickel. (b) Cumyl amine is also commercially available from TCI America: catalogue no. Li129.


(7) Ang, P. J. A.; Metallinos, C.; Snieckus, V., unpublished results.


(14) Metallinos, C.; Szillat, H.; Taylor, N. J.; Snieckus, V., manuscript in preparation.