SYNLETT
Spotlight 47

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research.

The N-Cumyl Group for Facile Manipulation of Carboxamides, Sulfonamides and Aryl O-Carbamates Post-Directed ortho Metallation

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Directed metalation groups (DMGs) are sometimes compromised by the inability to convert them to different functionalities under mild conditions in post-directed ortho metallation (DoM) steps.1 The advent of N-cumyl modified carboxamide, sulfonamide and O-carbamate DMGs,2 whose primary advantages over analogous N-t-Bu3 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 amine4 for access to benzamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary N-alkyl-N-cumyl amine5 for access to benzamides and sulfonamides, respectively, or by treating phenyl chloroformate with a secondary N-alkyl-N-cumyl amine 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-cumylbenzlamides and aryl O-carbamates may be easily decumylated1 under a number of conditions.5 Treatment of secondary N-cumylbenzlamides with a Lewis acid (BF3·OEt2/CH2Cl2/r.t.) gives primary amides in good yields, while application of Charette’s conditions6 (Tf2O/pyridine/CH2Cl2/-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 phthalamidine (2.2 equiv s-BuLi/TMEDA/THF/–78 °C) followed by electrophile quench gives, after oxidation (PDC/DMF/r.t.) access to 3-substituted phthalamides that can be decumylated (TFA/50 °C) in high yield. The method has been extended to TMS-protected sultams derived from N-cumylbenzenesulphonamide, 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 sultams (CF₃CHOH/reflux) provide direct access to 7-substituted benzoisothiazole-1,1-dioxides.

References

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. C129.