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* Metalation

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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* metalation (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 *O*-carbamates.

This Spotlight reviews several applications of *N*-cumyl-substituted functional groups in organic synthesis since the preliminary results of 1999.²

Scheme 1

Abstracts

ortho-Substituted *N*-cumylbenzamides and aryl *O*-carbamates may be easily decumylated³ under a number of conditions.² Treatment of secondary *N*-cumylbenzamides with a Lewis acid ($\text{BF}_3 \cdot \text{OEt}_2 / \text{CH}_2\text{Cl}_2 / \text{r.t.}$) gives primary amides in good yields, while application of Charette's conditions⁶ ($\text{Tf}_2\text{O} / \text{pyridine} / \text{CH}_2\text{Cl}_2 / -40^\circ\text{C}$) affords benzonitriles in one pot. Similarly, *O*-carbamates undergo rapid decumylation ($\text{TFA} / \text{r.t.} / 6\text{--}10\text{ min}$) to yield benzoxazines or secondary carbamates; the latter may be easily hydrolyzed to phenols ($10\% \text{ NaOH} / \text{EtOH} / \text{r.t.}$).

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/9–16 h) in high yield.² The method has been extended to TMS-protected sultams 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).⁷ Alternatively, decumylation of 7-substituted TMS-protected sultams (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*-acylimines (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.⁸

Clayden has used *N*-cumyl-*N*-benzylbenzamides to induce de-aromatizing cyclization reactions,⁹ 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 ($\pm$)-kainic acid,¹⁰ since the corresponding *t*-Bu³ analogue failed to dealkylate under identical conditions (TFA/reflux/6 h).

Enantioselective applications are also possible. *N*-Cumyl-*N*-ethylferrocenecarboxamide sterically mimics¹¹ *N,N*-diisopropylferrocenecarboxamide in (−)-sparteine-mediated metalation to provide 2-substituted ferrocenes in good yield. Unlike the original *N,N*-diisopropyl systems,^{12,13} the products are open to flexible manipulation by virtue of decumylation under very mild conditions (CF₃CH₂OH/reflux/5–12 h)³ to give, usually quantitatively, enantiomerically enriched secondary ferrocenecarboxamides for further transformations.¹⁴ For example, *N*-allylation of *N*-ethyl-2-vinylferrocenecarboxamide 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.¹¹

References

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