3,3,3-Bromodifluoro-1-propene: The Mild Introduction of CF₂

Paul R. Mears
School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK
paul.mears@manchester.ac.uk
Published online: 03.12.2014

Introduction

With the virtues of installing fluorine into organic compounds with potential pharmaceutical uses known,1 methods for introducing a CF₂ group under milder conditions are desirable and are more likely to find use in installing fluorne into advanced organic fragments of natural products and their analogues. One such reagent is 3,3,3-bromodifluoro-1-propene,2 which was first prepared in 1955 by a radi cal reaction of CF₂Br₂ and ethylene before base-mediated elimination.3 This (hazardous!) procedure was rediscovered by Seyferth et al.4 Lithiation of 3,3,3-bromodifluoro-1-propene gives difluoroallyllithium which reacts with electrophiles in the form of aldehydes, ketones or trialkylsilyl chlorides. The instability of difluoroallyllithium at temperatures >–95 °C has led to milder alternatives being developed, including work by Burton et al. where a screen of transition-metal-mediated coupling reactions with aldehydes and ketones concluded with zinc powder identified as the reagent of choice.5 More recently, the indium-mediated coupling6 has become the most widely used reaction for addition of (now widely commercially available) 3,3,3-bromodifluoro-1-propene to aldehydes and ketones in the preparation of difluorohomoallylic alcohols. The regioselectivity of these reactions is marked by the fact that the CF₂ terminus always forms the C–E bond (E = electrophile), resulting in a general formula (ECF₂CH=CH₂).

Table 1 Use of 3,3,3-Bromodifluoro-1-propene

(A) Qing et al. used the indium-mediated difluoroallylation reaction as a starting point in their synthesis of novel geminal-difluorinated sugar nucleosides.7 In fact, the reaction was diastereo-selective and gave the anti-homoallylic alcohol as the major product. Further steps were used to prepare Nⁱ-(3-deoxy-3,3-difluoro-D-arabinofuranosyl)cytosine.

(B) Taguchi and co-workers used the indium-mediated coupling conditions to prepare difluorohomoallylic alcohols before developing a reagent system to effect a defluorinative allylic alkylation transformation.8 The resulting fluoro-olefin structures are known isosteres for peptidic bonds.

(C) Zhao, Wang and co-workers reported the first preparation of difluorohomoallylic amines using their protocol of zinc-mediated coupling of 3,3,3-bromodifluoro-1-propene to α-amido sulfones.9

Paul Mears graduated with a first class honours degree in Applied Chemistry from the University of Leeds, UK in 2010. He subsequently moved to the University of Manchester, UK to pursue graduate studies under the supervision of Prof. Jim Thomas. His work is focused on natural product total synthesis, specifically of the bryostatin macrolides, as well as routes towards difluorinated analogues of these and related compounds.
(D) Qing and co-workers found that the use of a zinc-mediated coupling of 3,3,3-bromodifluoro-1-propene in the presence of catalytic SnCl2 gave the resulting homoallylic hydrazine in good yield and with high diastereoselectivity. Cleavage of the hydrazine enables facile accessibility to chiral difluorohomoallylic amines.

(E) Lin and Qing showed that the difluorohomoallylic alcohols and amines (prepared from the reactions shown above) could undergo an anti-Markovnikov hydroalkylation in the presence of an organozincate under palladium catalysis with an oxidant (benzoquinone under an air atmosphere).

(F) Zhang and co-workers directly coupled 3,3,3-bromodifluoro-1-propene to arylboronic acids with high regioselectivity (α-substitution) and chemoselectivity (aldehydes were unreacted under the reaction conditions).

(G) Ichikawa and co-workers found conditions for a selective γ-attack (SN2′) of 3,3,3-bromodifluoro-1-propene by 1,2-bromoheteroarenes to give 3,3-difluoroallylic compounds which could undergo an intramolecular radical cyclisation to gain access to 3-difluoromethylated dihydrobenzoheteroles.

References

(2) CAS no. 420-90-6