Tetrahedron Letters 54 (2013) 1897–1898

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An easy synthesis of α-trifluoromethyl-amines from aldehydes or ketones using the Ruppert-Prakash reagent

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ARTICLE INFO

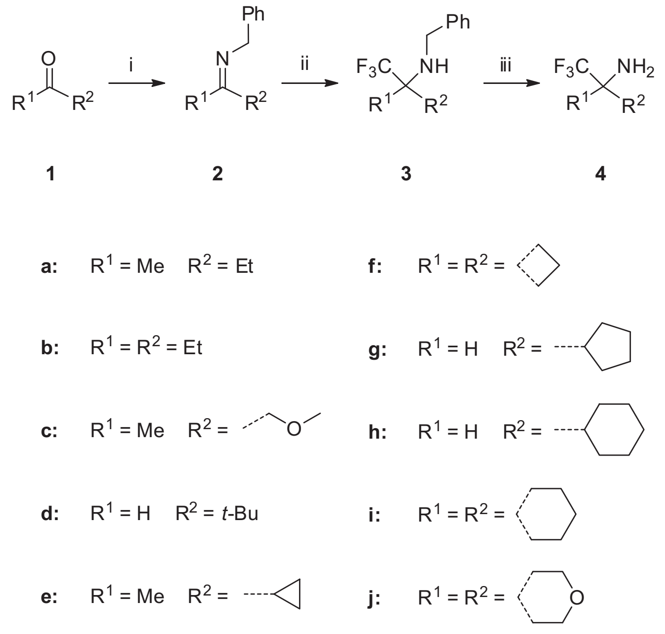
Article history:
Received 17 December 2012
Revised 21 January 2013
Accepted 31 January 2013
Available online 6 February 2013

Keywords:
Trifluoromethylation
Amines
Imines
Silicon
One-pot synthesis

ABSTRACT

A small library of structurally diverse primary amines bearing a geminal CF_3 group was synthesized on a preparative scale. The synthesis starts with an aldehyde or ketone that reacts with benzylamine yielding the corresponding imine. The latter is then trifluoromethylated with Me_3SiCF_3 under acidic conditions to give a benzylalkylamine. In the last step the Pd-mediated hydrogenation of the benzylalkylamines furnishes the title compounds. All synthetic steps are high-yielding; neither the isolation of the intermediates nor the chromatographic purification of the products is necessary.

Amines with a geminal trifluoromethyl group have attracted considerable attention in biochemistry as they are metabolically stable bioisosteres of the corresponding amides.[1] The majority of available synthetic approaches to α-trifluoromethylated amines involves the use of trifluoromethyl-substituted imines.[2] However, the preparation of the latter often constitutes a synthetic challenge on its own. An acid-catalyzed nucleophilic trifluoromethylation of various imines with Me_3SiCF_3, described in a recent report by Dilman and co-workers,[3] provides a better alternative to the aforementioned method. A number of structurally diverse secondary amines[3] (including cyclic examples[4]) bearing a geminal trifluoromethyl group were synthesized through this reaction. We have recently expanded the scope of Dilman's method to CF_3-functionalized primary amines by preparing two cyclobutane-based amino acids through the catalytic de-benzylation of the corresponding benzylalkylamine precursors.[5] However, the procedure involved chromatographic purification of the imine and benzylalkylamine intermediates. In the present Letter, we report an improved procedure giving an easy access to primary amines possessing a geminal trifluoromethyl group from readily available carbonyl compounds and benzylamine. As shown in



Scheme 1. The preparation of primary amines possessing a geminal trifluoromethyl group. Reagents and conditions: (i) benzylamine, rt, (ii) Me_3SiCF_3, KHF_2, TFA, (iii) H_2, 10% Pd/C.[6]

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0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.01.132

Scheme 1, the reaction of carbonyl compounds **1** with benzylamine readily gave imines **2**. The latter undergo an addition of Me_3SiCF_3 to yield benzylalkylamine **3**.

Notably, the two reaction steps can be carried out in one pot since the preparation of intermediate **2** only requires evaporation of the solvent and drying in vacuum.

The work-up after the second synthetic step was also straightforward (see SI for details). The crude benzylalkylamines **3** were then subjected to a Pd-mediated hydrogenolysis resulting in *gem*-trifluoromethylamines **4**. Compounds **4** were easily purified by recrystallization of their hydrochloride salts from acetonitrile. ^1H, ^{13}C, ^{19}F NMR, LC–MS, and elemental analyses data of compounds **4** confirmed their structures and high purity. The possibility to combine the two-step preparation of benzylalkylamines in one-pot along with no need for chromatographic purification of both the intermediates and the products make the described approach to these amines with a geminal trifluoromethyl group extremely straightforward. Multigram amounts of the target amines can be easily synthesized via this approach.

Acknowledgment

We thank Dr. A. D. Dilman for helpful discussions.

Supplementary data

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.132.

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6. In a typical reaction 0.243 mol of Ruppert-Prakash reagent was combined with 0.162 mol of freshly prepared imine **2** dissolved in CH_3CN/DMF (10:1) in the presence of a slight molar excess of TFA and a catalytic amount of KHF_2 at 0 °C. After 12 h of stirring at ambient temperature the mixture was triturated with saturated aqueous Na_2CO_3, diluted with H_2O and then extracted several times with EtOAc. Evaporation of the solvent resulted in crude benzylalkylamine **3** which was further purified by transformation into its hydrochloride salt followed by recrystallization from acetonitrile. Benzylalkylamine **3** was successfully de-benzylated through hydrogenation over Pd/C at 50 bar. For full experimental details see SI.