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Advances in the TBAF-induced aldol-type addition of α-trialkylsilyl-α-diazoacetones: TIPS versus TES

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ABSTRACT

α-Triisopropylsilyl-α-diazoacetone (TIPS-diazoacetone) underwent high-yielding "diazo-side" Mukaiyama aldol-type addition with a range of aryl and alkyl aldehydes when subjected to stoichiometric amount of tetrabutylammonium fluoride at −16 °C, in Et_2O. Robustness of the TIPS group makes TIPS-diazoacetone a stable surrogate for α-triethylsilyl-α-diazoacetone, on which generation of the corresponding carbanion can still be efficiently achieved under nucleophilic, weakly basic and practical conditions. These results highlight the synthetic potential that can be expected from TIPS-diazoacetone, promising building block for the convergent elaboration of highly functionalised versatile diazocarbonyl compounds.

1. Introduction

The synthesis and transformation of α-diazocarbonyl scaffolds have aroused a steady interest in organic synthesis for many years [1]. These scaffolds are versatile intermediates that can undergo a large array of transformations, especially on the reactive C=N_2 site, including oxidations, reductions, C–C, C–H, heteroatom-H insertions and cyclopropanations. Numerous strategies have been designed towards their formation [1,2]. Among them, oxidation of α-keto hydrazones has been successfully developed (Scheme 1, route *a*), although limited by the availability of the substrates. Acylation of diazomethane (route *b*) is classically used to access terminal diazoketones but suffers from safety hazards. Diazo-transfer, typically from sulfonyl azides (route *c*), has been applied to a large range of active methylene compounds to elaborate diverse diazodicarbonyl scaffolds, which upon deacylation can provide terminal diazoketones. Substitution at the diazo carbon of terminal diazoketones, commonly prepared via route *b* or route *c*, while preserving the diazo moiety, constitutes a convergent strategy to access diversely functionalised diazocarbonyl scaffolds (route *d*).

An important reaction in this field (route *d*) is the aldol-type addition between terminal diazoketones **1** and various aldehydes, in basic media, providing a convergent route to β-hydroxy-α-diazoketones **2** (Scheme 2a). Strong bases such as lithium diisopropylamide (LDA) are commonly used in stoichiometric amount, at low temperature, to perform this reaction [3,4]. We recently reported an alternative procedure using nucleophilic and weakly basic conditions, consisting of the tetrabutylammonium fluoride (TBAF)-triggered aldol-type addition between α-triethylsilyl-α-diazoacetone (TES-diazoacetone, **3**) and various aldehydes (Scheme 2b) [5]. A large range of β-hydroxy-α-diazoketones **4** could thus be synthesised under convenient experimental conditions.

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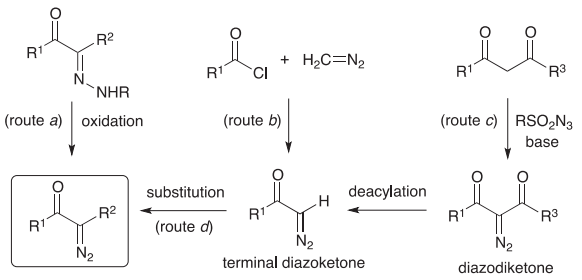


Scheme 1. Strategies towards the formation of diazoketone scaffolds.

Beside, TES-diazoacetone **3** revealed itself to be a useful three-carbon building block, which could be introduced into functionalised carbon chains *via* a LDA-induced double cross-aldol addition sequence (Scheme 3) [4]. The presence of the TES protecting group was crucial to carry out first the LDA-induced "methyl-side" aldolisation, without any competitive aldol-type addition on the more reactive "diazo-side". Methyl-side aldolisation resulted in a mixture of the *C*-silylated and *C*-desilylated aldols **5**. Methanolysis on the crude mixture achieved complete desilylation before the diazo-side aldol-type addition could be performed classically with LDA, at low temperature, to produce diazodiols **6** (Scheme 3). This sequence allowed the fragile β-hydroxy-α-diazoketone moiety of compounds **6** to be successfully generated in the last step.

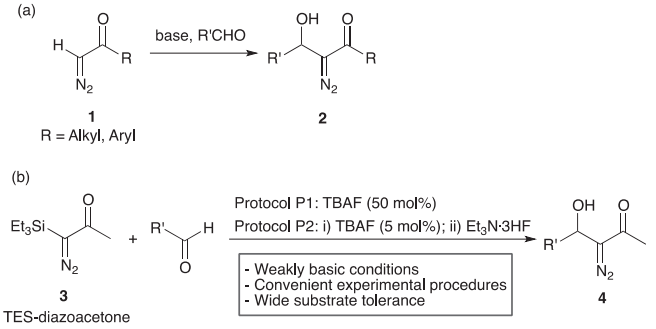
To explore further the potential of the α-trialkylsilyl-α-diazoacetone scaffold as a three-carbon building block, it appeared necessary to prevent unintentional diazo-side desilylation, which readily occurs with the labile TES group. Thus, we thought of replacing the TES protecting group by the more robust triisopropylsilyl (TIPS) one [6]. To assess the relevance of this scaffold, we needed to investigate if the diazo-side aldol-type addition could still be conveniently performed under nucleophilic activation by a fluoride. To this aim, we report here the behaviour of α-triisopropylsilyl-α-diazoacetone (TIPS-diazoacetone, **7**, Scheme 4) towards fluoride-induced aldol-type addition.

2. Results and discussion

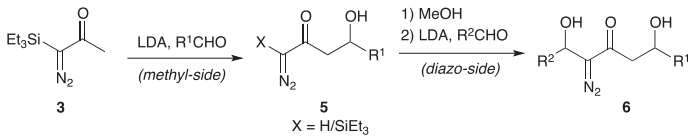
TIPS-diazoacetone **7** [7] was prepared in a good yield by silylation of diazoacetone, using TIPS triflate/*N*,*N*-diisopropylethylamine as the silylating system, at 0 °C (Scheme 4) [5,8]. Diazoacetone, stable yellow oil that can be stored in freezer for months, was prepared beforehand on a multigram scale by diazo-transfer from tosyl azide to acetylacetone [5,9], followed by deacetylation [4] (Scheme 4). We were pleased to observe that TIPS-diazoacetone was stable, storable for months in the freezer, contrary to TES-diazoacetone, which rapidly underwent desilylation/degradation in a few weeks time, even in the freezer.

We investigated first the fluoride-induced aldol-type reaction between TIPS-diazoacetone and benzaldehyde (Table 1). TBAF, the optimal source of fluoride highlighted for TES-diazoacetone [5], was initially selected and the best catalytic conditions were applied: TBAF 5 mol %, 4 Å molecular sieves (MSs), anhydrous Et_2O, −16 °C, 2 h (Table 1, entry 1). Unfortunately, very low conversion was achieved and aldol **4a**, contaminated by traces of bis-aldol **8a** (Scheme 5), was isolated in only 7% yield after column chromatography [10]. No *O*-TIPS–protected aldol was detected. This first result seems to exclude that a fluoride-triggered autocatalytic mechanism could proceed here. This hypothesis was supported by the fact that no reactivity was observed when TBAF was replaced by an equimolar amount of the tetrabutylammonium alkoxide of benzylic alcohol [11].

The use of an equimolar amount of TBAF (Table 1, entry 2) led to the formation of aldol **4a** and bis-aldol **8a** in a 9:1 ratio, from the ^{1}H NMR spectrum of the crude product (Scheme 5). Pure aldol **4a** was isolated in 67% yield after column chromatography. Bis-aldol **8a**, slightly more polar than aldol **4a**, could not be isolated and was recovered as a



Scheme 2. Base and fluoride-induced aldol-type additions on diazoketone scaffolds.



Scheme 3. TES-diazoacetone chain-extension by double cross-aldol addition sequence.