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Fluorinated hydrazones. Part 1: Reductive coupling reactions of chlorodifluoroacetylated dialkylhydrazones using tetrakis(dimethylamino)ethylene (TDAE)

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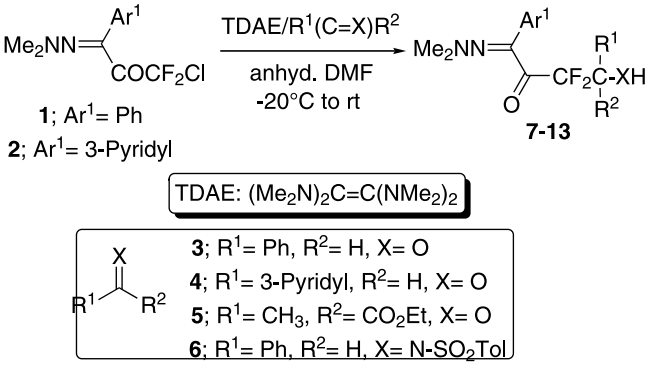
Abstract—A series of new α-diketone derived *gem*-difluorinated mono-hydrazone derivatives are easily obtained in moderate to good yields from the tetrakis(dimethylamino)ethylene-mediated reductive coupling reactions of chlorodifluoroacetylated dialkylhydrazones with aromatic aldehydes, ethyl pyruvate and an *N*-tosyl aldimine.

In order to prepare new fluorine-containing molecules having potential biological applications, we have recently reported a number of radical and anionic methodologies that can be used to prepare new fluorinated organic molecules.[1] Among such procedures developed in our laboratories, we have shown that aromatic and heterocyclic-CF_2X (X: Br, Cl), as well as trifluoromethyl iodide, can be used in conjunction with the electron-transfer agent, tetrakis-(dimethylamino)-ethylene (TDAE), to generate the respective, surprisingly stable anions,[2] which can be used in various nucleophilic substitution reactions. Hydrazones constitute an important class of compounds due to the rich chemistry of the hydrazono group, because of which, they have attracted a great deal of attention in recent years.[3] Synthetic applications of fluorinated hydrazones have been relatively less explored. Kamitori et al.[4] have shown that the dimethylhydrazone of aromatic and aliphatic aldehydes as well as formaldehyde dialkylhydrazones can be acylated with trifluoroacetic anhydride (TFAA) at the azomethine carbon. Some of the corresponding trifluoroacylated compounds have been used for the synthesis of a series of trifluoromethylated heterocycles.[5] Lassaletta et al.[6] similarly presented the 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones to fluoral (CF_3CHO) and an asymmetric version using chiral hydrazones. The same group also reported an enantioselective approach of α-hydroxy-α-trifluoromethyl hydrazones through the addition of chiral hydrazones to trifluoromethyl ketones.[7] Recently trifluoroacetaldehyde hydrazones have been proposed for the synthesis of CF_3-containing heterocycles[8] and for the asymmetric synthesis of α-trifluoromethyl-substituted primary amines.[9] Finally Okano et al. achieved the synthesis of optically active trifluoromethylated indolizidine derivatives via a stereoselective radical cyclization involving a trifluoroacetone SAMP-hydrazone as starting material.[10]



Scheme 1.

Keywords: hydrazones; tetrakis(dimethylamino)ethylene; electron transfer; fluorine and compounds.

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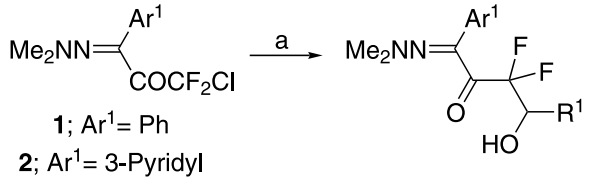
Within a project devoted to the synthesis of new building blocks and therapeutic agents, a mild and rapid approach for the synthesis of functionalized difluoromethylene aromatic and heterocyclic dialkylhydrazones was sought, in order to provide novel starting materials for chemical elaboration. We report here the synthesis of chlorodifluoroacetylated dialkylhydrazones **1**, **2**[11] and a new elaboration of our TDAE methodology to generate the corresponding difluoroacetyl anions, which undergo nucleophilic additions to heteroaryl aldehydes **3**, **4**, ethyl pyruvate **5** and *N*-tosyl aldimine **6** to give the corresponding new difluoromethylene derivatives **7**–**13** (Schemes 1–3).

As a model substrate, chlorodifluoroacetylated hydrazone **1** was treated with 3 equivalents of benzaldehyde **3** in the presence of TDAE (1 equiv.) in anhydrous DMF at –20°C; TLC and fluorine NMR analysis showed that the reaction was slower compared to the reaction involving aromatic-$COCF_2Cl$ derivatives. Usually, stirring at –20°C for 1 h followed by 18 h at room temperature was necessary for a complete conversion of the starting material. This is attributed to the fact that these hydrazones, because of their relatively electron-rich character, are probably poorer electron-acceptors than the chlorodifluoroacetylated ketones[2d] or the bromodifluoromethylated heterocycles[2e] [as judged by their reduction potentials measured by cyclic voltammetry in DMF/NBu_4PF_6 0.1 M; glassy carbon electrode, Ep_1 (first peak potential) = –1.66 V/SCE for **1** and Ep_1 = –1.50 V/SCE for **2**]. The corresponding carbinol **7** was obtained in 57% isolated yield after silica gel chromatography. Reaction with hydrazone **2** was more efficient and needed only 8 h stirring at room temperature for complete conversion affording addition product **9** in 68% isolated yield (Scheme 2).[12]



1; Ar^1 = Ph

2; Ar^1 = 3-Pyridyl

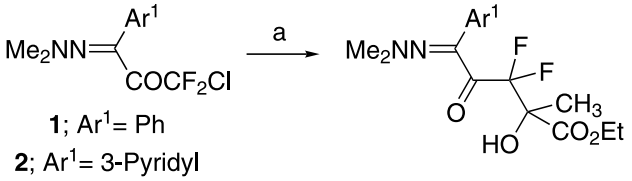
a. TDAE (1 equiv.)/R^1CHO **3**, **4** (3 equiv.) anhyd. DMF/- 20°C to rt

7; $Ar^1 = R^1$ = Ph; - 20°C/1 h; rt 18 h, 57%

8; Ar^1 = Ph, R^1 = 3-Pyridyl; - 20°C/1 h; rt 18h, 61%

9; Ar^1 = 3-Pyridyl, R^1 = Ph; - 20°C/1 h; rt 8 h, 68%

Scheme 2.



1; Ar^1 = Ph

2; Ar^1 = 3-Pyridyl

a. TDAE (1 equiv.)/CH_3COCO_2Et **5** (3 equiv.) anhyd. DMF/- 20°C to rt

10; Ar^1 = Ph; - 20°C/1 h; rt 24 h; 42%

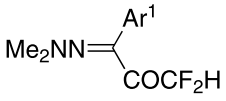
11; Ar^1 = 3-Pyridyl; - 20°C/1 h;rt 24 h; 53%

Scheme 3.

The TDAE-mediated reductive coupling studies were extended to the use of ethyl pyruvate **5** as the electrophile. We obtained the corresponding hydroxy ester derivatives **10** and **11** in 42% and 53% isolated yields, respectively. Required reaction times were found to be longer than those needed for the heteroaldehydes (–20°C /1 h and 24 h at room temperature, Scheme 3).

Recently Prakash et al.[13] reported that $TMSCF_3$ and tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT) could be used for the efficient nucleophilic trifluoromethylation of *N*-tosylaldimines. Such readily available aldimines, prepared in good yields following a recent procedure described by Chemla et al.,[14] were also found to be good electrophiles in the reaction with the carbanions derived from hydrazones **1** and **2**. The corresponding sulfonaldimines **12** and **13** were obtained in good yields (**12**: 65%; **13**: 62%) after stirring at –20°C for 1 h, and then at room temperature for 18 h (Scheme 4). These molecules are potentially useful for the synthesis of novel $COCF_2$-containing amines.

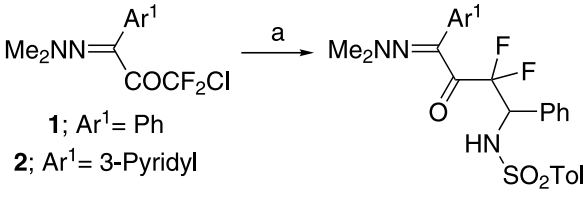
In all the reactions presented here, the remaining balance of material was found to be the corresponding $COCF_2H$ hydrazones **14** and **15**.



14; Ar^1 = Ph

15; Ar^1 = 3-Pyridyl

In conclusion, we have shown that, in conjunction with the electron-transfer agent, TDAE, chlorodifluoroacetylated dialkylhydrazones are good sources of difluoroketoenolate carbanions that have been shown to undergo nucleophilic addition reactions with a series of electrophiles. The yields were mostly good, but have not yet been optimized. All the products are new and potentially useful for chemical elaboration. Work is in progress in this direction as well as toward



1; Ar^1 = Ph

2; Ar^1 = 3-Pyridyl

a. TDAE (1 equiv.)/PhCH=NSO_2Tol **6** (3 equiv.) anhyd. DMF/- 20°C to rt

12; Ar^1 = Ph; - 20°C/1h; rt 18h; 65%

13; Ar^1 = 3-Pyridyl; - 20°C/1h; rt 18h; 62%

Scheme 4.

the extension of this chemistry to other chlorodifluoroacetylated hydrazones.

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11. Hydrazones **1** (yellow solid; mp 75°C) and **2** (orange viscous oil) were prepared in 62% and 71% isolated yields, by chlorodifluoroacetylation of the corresponding hydrazones using chlorodifluoroacetic anhydride (CDFAA/2 equiv.) and 2,6-lutidine (2 equiv.) in anhydrous dichloromethane (0°C/1 h and room temperature for 3 h) following the procedure described in Ref. 4a for the trifluoroacetylated analogs.
12. A typical reaction: Hydrazone **1** (0.30 g, 1.15 mmol) and 3-benzaldehyde **3** (0.37 g, 3.45 mmol, 3 equiv.) were mixed in anhydrous DMF (5 ml) under nitrogen. The solution was cooled to −20°C and maintained at this temperature for 30 min and was then added dropwise (via a syringe) to TDAE (0.23 g, 0.27 ml, 1.15 mmol). A red color immediately developed with the formation of a fine white precipitate. The solution was vigorously stirred at −20°C for 1 h and then warmed up to room temperature for 18 h. After this time TLC analysis (CH_2Cl_2/EtOAc, 7/3) clearly showed that **1** had been totally consumed. The orange–red turbid solution was filtered (to remove the octamethyloxamidinium dichloride) and hydrolyzed with 25 ml of brine. The aqueous solution was extracted with CH_2Cl_2 (3×50 mL), the combined organic layers washed with brine (3×50 ml), H_2O (3×50 mL) and then dried over $MgSO_4$. Evaporation of the solvent left an orange viscous liquid as the crude product. Purification by silica gel chromatography (CH_2Cl_2/EtOAc, 8/2) gave 0. 215 g (0.65 mmol; 57%) of a yellowish viscous oil of **7**. **1-(Dimethyl-hydrazono)-3,3-difluoro-4-hydroxy-1,4-diphenyl-butan-2-one**. ^{1}H NMR (300 MHz/$CDCl_3$): δ_H 2.48 (6H, s, CH_3), 5.21 (1H, brs, OH), 5.42–5.60 (1H, dd, J=16.5, 6.9 Hz, -C*H*OH), 7.20–7.68 (3H, m, H-arom), 7.61–7.78 (5H, m, H-arom), 8.01–8.06 (2H, m, H-arom). ^{19}F NMR (282 MHz/$CDCl_3$/$CFCl_3$): δ_F −106.92 (1F, dd, J=266, 6.8 Hz), −113.52 (1F, dd, J=266, 16.4 Hz). HRMS (CI): calcd for $C_{18}H_{18}F_2N_2O_2$: 332. 1336 (MH+); found 332. 1348.
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