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Journal of Fluorine Chemistry 123 (2003) 61–63
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

Preparation of TMS protected trifluoromethylated alcohols using trimethylamine *N*-oxide and trifluoromethyltrimethylsilane ($TMSCF_3$)

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Received 12 February 2003; received in revised form 4 April 2003; accepted 4 April 2003

Dedicated to Professor Eric Banks on the occasion of his 70th birthday

Abstract

A catalytic trifluoromethylation of aldehydes using trimethylamine *N*-oxide and trifluoromethyltrimethylsilane ($TMSCF_3$) is described. Aromatic, aliphatic and α,β-unsaturated aldehydes provided good to excellent yields of the corresponding trifluoromethylated products.

Keywords: Aldehydes; Trifluoromethyltrimethylsilane; Trimethylamine *N*-oxide; Catalytic CF_3 transfer; Nucleophilic trifluoromethylation

1. Introduction

After our initial discovery in 1989 [1], $TMSCF_3$ has been developed into a versatile reagent for the facile introduction of the trifluoromethyl moiety into organic molecules. In general carbonyl compounds, esters, activated imines and related electrophiles undergo smooth reaction under the initiation by fluoride sources [2,3]. A variety of fluoride sources such as organic TBAF, TBAT, TMAF as well as CsF have proven to be efficient in various cases. Metal alkoxides were also found as initiators for the nucleophilic trifluoromethylation reactions [1]. Although, the yields of the trifluoromethylated adducts with a variety of electrophiles were high, the reactions were not catalytic in initiators. Furthermore, due to the basic nature of these initiators we sought a milder process. A true catalytic process of stereoselective trifluoromethylation reaction is yet to be realized.

Recent advances in Lewis base catalyzed organic transformation for the silylated species [4] that take advantage of the high strength of the Si–O bond as well as judicious selection of kinetic reactivity can also be applied to trifluoromethyltrimethylsilane ($TMSCF_3$) chemistry [2]. We have envisioned that we would be able to activate $TMSCF_3$ for trifluoromethide transfer to the carbonyl compounds in a similar fashion using oxygen nucleophiles that can act as true catalysts. Our final aim is to eventually use this chemistry to achieve facile enantioselective CF_3 transfer [5]. Here we disclose our preliminary results towards this approach.

2. Results and discussion

To validate our outlined approach we have screened the reactivity of commercially available amine oxides such as pyridine *N*-oxide, *p*-chloropyridine *N*-oxide, *N*,*N*-dimethylpyridine *N*-oxide as well as hexamethylphosphoramide. Attempts with stoichiometric amounts of HMPA gave only <10% conversion after 48 h with representative aldehyde **1a**. The probable explanation for this low yield conversion is the poor electrophilicity of $TMSCF_3$. Though it is hard to find a system more nucleophilic than HMPA, we expected that trialkyl amine *N*-oxides to be more nucleophilic compared to aromatic *N*-oxides and therefore we tested the use of trimethylamine *N*-oxide for the activation of $TMSCF_3$. In fact in the presence of stoichiometric amount of trimethylamine *N*-oxide complete conversion of the aldehyde **1a** to the corresponding TMS protected alcohol **2a** was observed. It is very important to note that no free alcohol was observed, indicating true catalysis (vide supra). Further study of the reaction conditions significantly lowered the amount of amine oxide to 50 mol%. A typical reaction procedure is reported in Section 4. Table 1 shows the scope of the reaction

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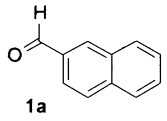
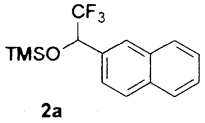
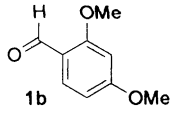
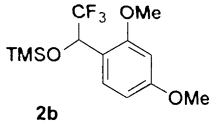
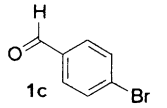
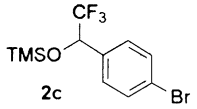
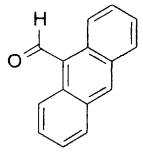
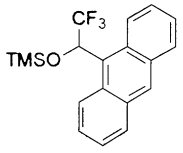
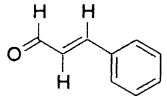
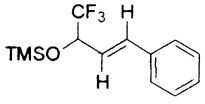
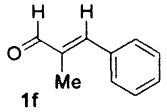
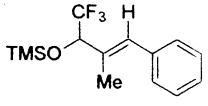
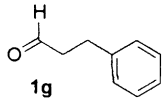
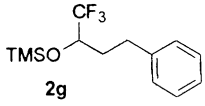
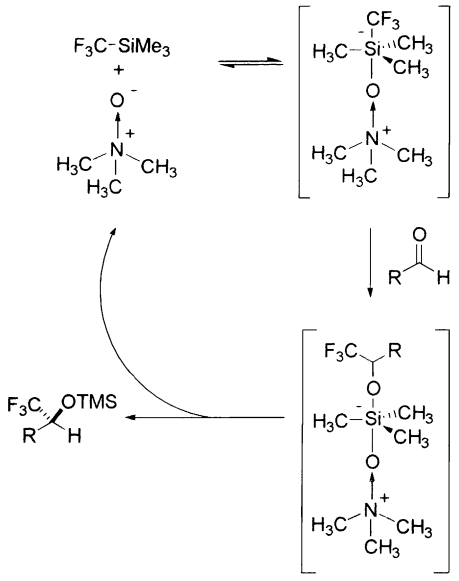
0022-1139/$ – see front matter
doi:10.1016/S0022-1139(03)00104-0

Table 1
Trifluoromethylation of aldehydes using trimethylamine oxide

Entry	Aldehydes	TMS protected alcohols	Yields (%)
1	 **1a**	 **2a**	77
2	 **1b**	 **2b**	80
3	 **1c**	 **2c**	76
4	 **1d**	 **2d**	85
5	 **1e**	 **2e**	74
6	 **1f**	 **2f**	79
7	 **1g**	 **2g**	55



Scheme 1.

and yields of the products. As it is evident from entry 2, there is no significant influence of bulky substitutents on the reaction yield. Aromatic aldehydes with electron withdrawing as well as electron donating groups react equally well in the amine oxide catalyzed reaction. Aldehyde with α protons **1g** provides the product **2g** without any side reaction albeit in moderate yield. The probable path for the observed catalysis by trimethylamine oxide is depicted in Scheme 1.

We propose that trimethylamine oxide-complexed $TMSCF_3$ **3** is in equilibrium with the starting materials and this complex trifluoromethylates the aldehydes to generate the complex **4**, which on fragmentation provides the TMS protected alcohols and amine oxide. The reaction however, is very sluggish with ketones due to their low electrophilicity.

3. Conclusions

In summary, we have developed an efficient catalytic method for the preparation of TMS protected trifluromethylated alcohols from a variety of aldehydes using trimethylamine *N*-oxide as a recoverable nucleophilic catalyst. The present methodology is applicable for base sensitive substrates. Our studies to apply this reaction to asymmetric synthesis using chiral amine oxides is currently underway.

4. Experimental

4.1. Typical reaction procedure for amine oxide catalyzed $TMSCF_3$ addition to carbonyl compounds

In a flame dried flask were taken 1 mmol of aldehyde and 0.5 mmol of trimethylamine oxide in 6 ml dry THF and stirred for 0.5 h. Subsequently, 3 mmol of neat $TMSCF_3$ was added to the reaction mixture. The flask was closed with a rubber septum and the reaction mixture was stirred for 12 h at room temperature. After all the starting material was consumed, the reaction mixture was evaporated to dryness and the residue was washed several times with diethyl ether. Further recrystallization from ether or flash chromatography afforded the pure TMS protected alcohols. Melting points reported are uncorrected.

2a: White solid, mp 62 °C, ^{1}H NMR (300 MHz, $CDCl_3$ as solvent and TMS as standard): δ 0.13 (s, 9H), 5.08 (q, $J = 6.8$ Hz, 1H), 7.40–7.61 (m, 3H), 7.82–7.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$ as solvent and TMS as standard): δ −0.24, 73.48 (q, ^2J(C, F) = 32.2 Hz), 124.3 (q, ^1J(C, F) = 282 Hz), 124.8, 126.3, 126.6, 127.3, 127.7, 128.1, 128.2, 132.9, 133.0, 133.7; ^{19}F NMR (282.2 MHz, $CDCl_3$ as solvent and $CFCl_3$ as standard): δ −78.6 (^3J(F, H) = 5.1 Hz); HRMS (EI) *m/z* 298.1004, calcd for $C_{15}H_{17}F_3OSi$ 298.1001.

2b: Yellowish liquid, ^{1}H NMR δ 0.09 (s, 9H), 3.77 (s, 3H), 3.79 (s, 3H), 5.51 (q, $J = 6.5$ Hz, 1H), 6.80–6.88 (m, 2H), 7.15 (m, 1H); ^{13}C NMR δ −0.401, 55.6, 56.2, 65.9 (q, ^2J(C, F) = 32.7 Hz), 111.8, 114.3, 115.2, 124.5 (q, ^1J(C, F) = 283 Hz), 151.1, 153.7; ^{19}F NMR δ −78.9 (^3J(F, H) = 5.9 Hz); HRMS (EI) *m/z* 308.1061, calcd for $C_{13}H_{19}F_3O_3Si$ 308.1055.

2c: Colorless liquid, ^{1}H NMR δ 0.122 (s, 9H), 4.87 (q, $J = 6.7$ Hz, 1H), 7.32 (d, $J = 7.79$ Hz, 2H), 7.51 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR δ −0.33, 72.2, (q, ^2J(C, F) = 32.3 Hz), 123.3, 123.8 (q, ^1J(C, F) = 282 Hz), 129.2, 131.5, 134.5; ^{19}F NMR δ −79.0 (^3J(F, H) = 6.0 Hz); HRMS (EI) *m/z* 327.9933, calcd for $C_{11}H_{14}F_3OSiBr$ 327.9929.

2d: Off white solid, mp 103–104 °C, ^{1}H NMR δ 0.026 (s, 9H), 6.56 (q, $J = 7.7$ Hz, 1H), 7.47–7.61 (m, 4H), 8.03 (d, $J = 8.53$, 1H), (d, $J = 8.28$ Hz, 1H), 8.20 (d, $J = 8.6$ Hz, 1H), 8.53 (s, 1H), 9.08 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR δ −0.628, 70.4 (q, ^2J(C, F) = 34 Hz), 122.3, 124.6, 125.0, 125.4, 125.5 (q, ^1J(C, F) = 281 Hz), 127.1, 127.9, 128.7, 129.7, 130.3, 130.5, 130.9, 131.2, 131.9; ^{19}F NMR δ −74.78 (^3J(F, H) = 7.44 Hz); HRMS (EI) *m/z* 348.1159, calcd for $C_{19}H_{19}F_3OSi$ 348.1157.

2e: Pale yellow liquid, ^{1}H NMR δ 0.206 (s, 9H), 4.58 (m, 1H), 6.18 (dd, $J = 15.8$ Hz, $J = 6.35$ Hz), 6.76 (d, $J = 16.41$ Hz, 1H), 7.27–7.43 (m, 5H); ^{13}C NMR δ −0.123, 72.23 (q, ^2J(C, F) = 32.7 Hz), 122.4, 124.2, (q, ^1J(C, F) = 283 Hz), 126.8, 128.4, 128.7, 134.9, 135.7; ^{19}F NMR δ −79.14 (^3J(F, H) = 6.3 Hz); HRMS (EI) *m/z* 274.0993, calcd for $C_{13}H_{17}F_3OSi$ 274.1000.

2f: Yellowish liquid, ^{1}H NMR δ 0.0 (s, 9H), 1.74 (s, 3H), 4.23 (q, $J = 6.9$ Hz, 1H), 6.43 (s, 1H), 7.05–7.19 (m, 5H); ^{13}C NMR δ −0.269, 13.6, 76.7 (q, ^2J(C, F) = 31 Hz), 124.5 (q, ^1J(C, F) = 283 Hz), 127.1, 128.2, 129.0, 131.2, 132.6, 136.6; ^{19}F NMR δ −77.24 (^3J(F, H) = 6.5 Hz); HRMS (EI) *m/z* 288.1158, calcd for $C_{14}H_{19}F_3OSi$ 288.1157.

2g: Yellow liquid, ^{1}H NMR δ 0.164 (s, 9H), 1.94 (m, 2H), 2.61 (m, 1H), 2.82 (m, 1H), 3.91 (m, 1H), 7.17–7.30 (m, 5H); ^{13}C NMR δ −0.40, 31.1, 32.2, 70.5 (q, ^2J(C, F) = 32.7 Hz), 125.5 (q, ^1J(C, F) = 283 Hz), 126.2, 128.3, 128.5, 140.7; ^{19}F NMR δ −79.2 (^3J(F, H) = 6.78 Hz); HRMS (EI) *m/z* 276.1153, calcd for $C_{13}H_{19}F_3OSi$ 276.1157.

Acknowledgements

Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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