Pergamon

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Tetrahedron Letters 44 (2003) 2799–2801

TETRAHEDRON LETTERS

Reactions of trifluoroamine oxide: a new method for selective fluorination of 1,3-diketones and β-ketoesters

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Received 1 February 2003; revised 19 February 2003; accepted 19 February 2003

Abstract—Fluorination of 1,3-diketones and β-ketoesters with trifluoroamine oxide in the presence of tetrabutylammonium hydroxide (TBAH) provides a one step route to mono- and difluoro-products selectively fluorinated at the α-position in good yields.

Of special importance to the growth of the fluorochemicals industry has been the dramatic changes in the physical and biological properties and chemical reactivities of organic materials that result from the introduction of fluorine as is evidenced by an amazingly diverse and constantly expanding range of commercial products. These changes have been exploited particularly in the fields of pharmaceutical, agrochemical and polymer chemistry.[1–3] The efficacy of many pharmaceuticals and agrochemicals is often enhanced by or are dependent on the presence of a single fluorine atom in the molecular structure.[4] Frequently such compounds can be synthesized from smaller molecules where fluorine is located at a specific site or often it is desirable to introduce the element directly in order to obtain the desired chemical composition.[5,6] Electrophilic fluorination is one of the most direct methods for selective introduction of fluorine into organic compounds. Elemental fluorine itself is one of the most powerful reagents.[7] However, fluoroxy compounds such as CF_3OF, $CF_3C(O)OF$, $CsSO_4F$, or $CH_3C(O)OF$, some of which were generated in situ, proved to be exciting reagents for the introduction of fluorine electrophilically into a wide variety of organic compounds.[8] The rather hazardous perchloryl fluoride has lost favor to other electrophiles including xenon difluoride that has been employed as a particularly interesting and easily handled source of electrophilic fluorine.[9] More recently much attention has been given to the fluoronitrogen compounds including *N*-substituted fluoropyridinium and *N*,*N*′-difluorobipyridinium salts, such as *N*,*N*′-difluorobipyridinium tetrafluoroborate (Daikin MEC-31™),[10,11] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Air Products Selectfluor™).[12,13] While the latter two reagents are readily available commercially, unfortunately some of the most powerful electrophilic NF reagents, e.g. the perfluoroalkylsulfonimides ($R_fSO_2N(F)SO_2R_f'$), have not been commercialized.[14–17] These N–F compounds are generally somewhat less reactive than the other reagents described above but nevertheless have proved to be particularly useful with a wide range of organic nucleophiles including β-dicarbonyl compounds both as enolates and neutural compounds.

We have now demonstrated the efficacy of another N–F reagent, trifluoroamine oxide (NF_3O), in controllably introducing fluorine into 1,3-diketones and β-ketoesters. In our earlier studies with this versatile electrophile, we found that it was a very effective fluorinating and nitrosating reagent in reaction with acyclic secondary alkyl amines.[18,19] Additionally, a series of pyrimidine methyl and polyfluoroalkyl ethers were synthesized from the reactions of this reagent with several 5-substituted uracils in the presence of non-fluorinated and polyfluorinated alcohols under basic conditions.[20] The application of NF_3O for the electrophilic fluorination of carbanionic organic substrates provides a simple straightforward one-step route for introducing fluorine at the α-position in 1,3-dicarbonyl compounds and in β-ketoesters. When the methylene group is unsubstituted, either one or two fluorine atoms may be introduced selectively under mild conditions and in high yields.

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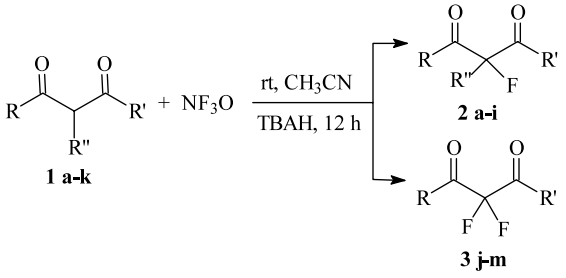
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00467-2

The usual experimental procedure was as follows. Into a dry 250 mL round-bottomed Pyrex flask equipped with a Teflon stopcock was placed a solution of [$CH_3C(O)CHClC(O)CH_3$] (1 mmol) and tetrabutyl ammonium hydroxide (TBAH) (1 mmol) in anhydrous acetonitrile (10 mL). The flask was cooled to −196°C and evacuated. Then it was warmed to −5°C and slightly more than the required amount of trifluoroamine oxide (>1 mmol) was added via vacuum transfer by slowly titrating the NF_3O into the vessel. A Plexiglass shield and gloves protect the worker. The mixture was warmed to room temperature and was stirred for 12 h. The solvent and any volatile materials were removed under vacuum (vacuum line) leaving the nonvolatile product.[20] Purification was brought about via column chromatography (silica gel, CH_3CN/$CH_3COOC_2H_5$, 7:3). Compound **2b** was obtained in 80% yield. Under similar reaction conditions, the other β-diketones were converted into analogous monofluoro diketones. This stoichiometry was utilized when R″ = CH_3 or Cl or R″ = H to introduce only a single fluorine atom (Scheme 1; Table 1 compounds **2a**–**i**).[22–26] However, when R″ = H and difluorination was the desired result, twice the amount of trifluoroamine oxide was used to ensure the formation of α,α-difluoro compounds (Scheme 1; Table 1 compounds **3j**–**m**).[27,28] In the latter case, very often a mixture of mono- and difluoro-compounds was obtained. Purification resulted from column chromatography as above. The pure products were identified by comparison with literature data. New compounds (**3l** and **3m**) were characterized by spectroscopic and high resolution mass spectrometric analyses.



Scheme 1.

Among the most striking features of these reactions is the uniformly high yield and almost complete absence of tar formation in spite of room temperature reaction conditions. At the end of the process, all of the monofluorinated products existed in the keto form and no change was observed upon workup. In general, not surprisingly, the 1,3-diketones are more reactive than the corresponding ketoesters and, in either case, the presence of the first fluorine atom on the α-carbon tends to discourage or at least reduce the rate of the replacement of the second hydrogen atom as the nucleophilicity of the α-carbon is reduced. This behavior is observed in similar reactions with other electrophilic fluorinating reagents as well. 1,3-Diketoesters, such as dimethylmalonate, failed to react under these conditions.

Preliminary results suggest that fluorination of the α-carbon of metal β-diketonates with NF_3O occurs without decomposition. Work is continuing on this series.

This present report once again describes the versatility of NF_3O as a powerful and manageable electrophilic fluorinating agent, in this case, to prepare monofluoro- and difluoro-diketones and ketoesters.

Caution: Trifluoroamine oxide is a strong oxidizer. While we have not experienced any problems, mixtures with organic materials are potentially explosive. Attempts to scale up the synthetic methods presented in

Table 1. Electrophilic fluorination of 1,3-diketones and β-ketoesters with NF_3O[a]

	Substrate (**1**)			Product	Conversion (%)	Yield (%)
	R	R′	R″			
a	CH_3	CH_3	CH_3	**2a**[b]	95	80
b	CH_3	CH_3	Cl	**2b**[b,c]	90	80
c	CH_3	OC_2H_5	Cl	**2c**[b,c]	90	80
d	CH_3	OC_2H_5	CH_3	**2d**[b]	95	80
e	CH_3	OC_4H_9	CH_3	**2e**[b]	90	80
f	CH_3	OC_2H_5	H	**2f**[b]	95	85
g	CH_3	C_2H_5	H	**2g**[b,d]	95	85
h	CH_3	CH_3	H	**2h**[b]	95	85
i	Ph	OC_2H_5	H	**2i**[b]	95	85
h	CH_3	CH_3	H	**3j**[d]	95	85
i	Ph	OC_2H_5	H	**3k**[e]	95	85
j	*c*-C_4H_3S	CF_3	H	**3l**[f]	95	85
k	*c*-C_4H_3O	CF_3	H	**3m**[f]	95	95

[a] All the reactions were carried out in acetonitrile.
[b] Ref. 22.
[c] Ref. 15.
[d] Ref. 21.
[e] Ref. 23.
[f] New compounds, see Refs. 27 and 28.

this paper should be avoided. Appropriate safety precautions must be observed when these reactions are carried out.

Acknowledgements

We are grateful to the National Science Foundation (Grant No. CHE-9720365) for support. O.D.G. is appreciative to the University of Rajasthan, Jaipur, India, for academic leave to carry out this work. Thanks are due Dr. Gary Knerr for HRMS measurements.

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24. $C_5H_6ClFO_2$ (**2b**):[15] ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.45 (d, CH_3, $J=2.5$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$): δ −126.2 (septet, $J=2.6$ Hz); MS (EI) m/e (species, intensity): 152 (M^+, 35), 117 (M^+−Cl, 70), 110 (M^+−$COCH_2$, 40), 43 (CH_3CO^+, 100); IR (KBr plates, cm^{-1}): ν 2925 vs, 1738 vs, 1618 s, 1361 w, 1256 vs, 1179 s, 1030 s, 1150 s, 882 w, 852 w.
25. $C_6H_8ClFO_3$ (**2c**):[15] ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, CH_3CH_2, $J=7.1$ Hz), 2.46 (d, CH_3CO, $J=2.6$ Hz), 4.39 (q, CH_3CH_2, $J=7.3$ Hz); ^{19}F NMR (188 MHz, $CDCl_3$): δ −123.82 (broad m); MS (EI) m/e (species, intensity): 182 (M^+, 15), 147 (M^+−Cl, 35), 139 (M^+−CH_3CO, 39), 43 (CH_3CO^+, 100); IR (neat, KBr plates, cm^{-1}): ν 2980 vs, 1761, 1618 s, 1362 m, 1256 vs, 1178 s, 1029 s, 1150 s, 882 w, 854 w.
26. $C_6H_9FO_2$ (**2g**):[21] ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (d, 3H, $J_{CH_3-CF}=21.1$ Hz), 2.27 (s, 3H, CH_3), 2.29 (s, 3H, CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ −157.87 (q); MS (EI) m/e (species, intensity): 132 (M^+, 54.6), 112 (M^+−HF, 40), 90 (M^+−CH_2CO, 45), 43 (CH_3CO^+, 100); IR (neat, KBr plates, cm^{-1}): ν 3137 vs, 2943 s, 1725 s, 1709 vs, 1467 s, 1262 s, 1163 m, 1079 m, 1020 vs, 908 m, 883 s, 773 s.
27. $C_8H_3F_5O_2S$ (**3l**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (m, 2H), 7.20 (m, 1H), 6.5 (m, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) ($CFCl_3$ external reference): δ −114.95 (CF_2), −81.82 (CF_3); IR (neat, KBr plates, cm^{-1}): ν 3088 vs, 1672 vs, 1514 m, 1414 s, 1354 s, 1251 s, 921 m, 854 s; HRMS calcd for $C_8H_3F_5O_2S$: 257.9774; found: 257.9757.
28. $C_8H_3F_5O_3$ (**3m**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53 (m, 1H), 7.41 (m, 1H), 6.96 (m, 1H); ^{19}F NMR (188 MHz, $CDCl_3$) ($CFCl_3$ external reference): δ −116.73 (CF_2), −81.82 (CF_3); IR (KBr plates, neat, cm^{-1}): ν 3137 vs, 2943 s, 1693 vs, 1467 s, 1262 s, 1163 m, 1079 m, 1020 vs, 908 m, 883 s, 773 ms; HRMS calcd for $C_8H_3F_5O_3$: 242.0002; found: 242.0010.