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Effect of sodium naphthalenide, a key SET reagent, on trifluoroacetyl derivatives

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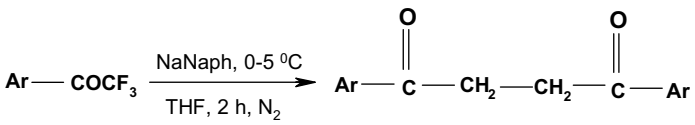
Abstract—Aromatic trifluoroacetyl derivatives on treatment with single electron transfer (SET) reagent, sodium naphthalenide, yield symmetrical defluorinated dimers, whereas for aliphatic trifluoroacetyl compounds the reaction usually fails. Investigations have been made for different substituents as well as for similar types of chloro and bromo compounds to establish the scope of the reaction.

Organic reactions through a single electron transfer (SET) mechanism have received increasing interest in recent years. Among several SET reagents, sodium naphthalenide has attracted special attention due to its cost effectiveness as well as easy availability. A number of reactions have been reported[1–6] where sodium naphthalenide has been used successfully as a SET reagent. As a part of our investigations in this field,[7–12] we have reported the effect of sodium naphthalenide on various heterocycles. In this connection, we have recently reported[13] the reaction of sodium naphthalenide (NaNaph) with 3-trifluoroacetylindole, which yielded a symmetrical dimeric compound as the sole product. The interesting aspect of this reaction is that though the starting material is a fluorinated compound, the symmetrical dimer is totally lacking fluorine as confirmed by F^{19} NMR spectroscopy. Based on this observation, we become interested in studying the effect of NaNaph on different trifluoroacetyl systems in order to see whether dimeric defluorinated products would be produced in other cases or the action of NaNaph on 3-trifluoroacetylindole was a special case.

In this investigation, a solution (deep green in color) of NaNaph was prepared at 0 °C by treating sodium with naphthalene in dry THF under nitrogen. A solution of the substrate in THF was then added dropwise to the sodium naphthalenide solution with stirring for 2 h at 0–5 °C and the progress of the reaction was monitored by TLC.[14] It was found that, for all the aromatic (both carbocyclic and heterocyclic) derivatives, the reaction proceeded well (Scheme 1) whereas aliphatic trifluoroacetyl derivatives, for example, ethyl, isopropyl, and *n*-butyl trifluoroacetyl compounds did not take part in



Scheme 1.

Keywords: Sodium naphthalenide; SET; Trifluoroacetyl; Aromatic heterocycles.
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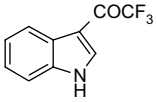
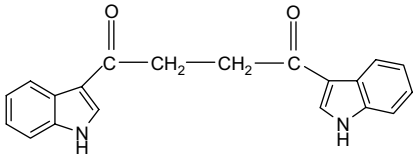
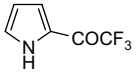
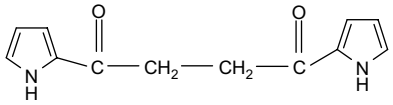
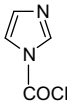
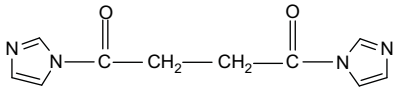
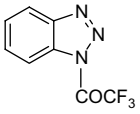
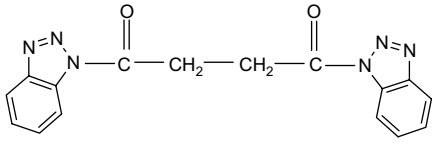
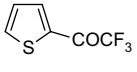
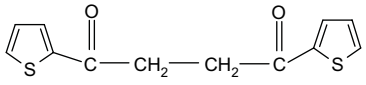
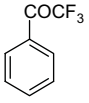
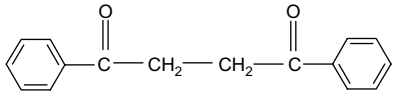
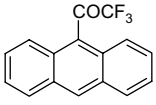
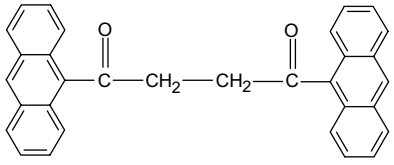
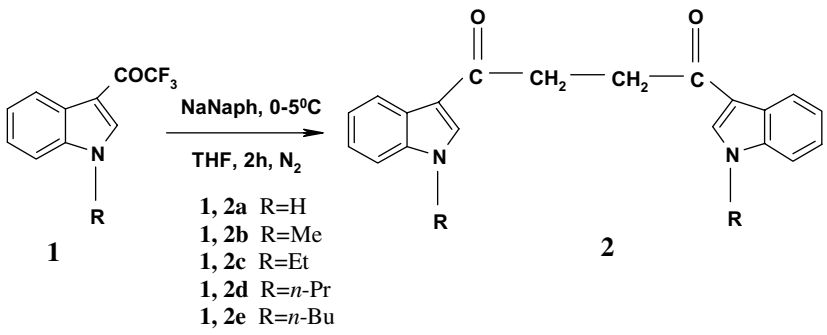
the reaction at all even after lengthening the reaction time. The reaction between methyl trifluoroacetyl derivative viz. 1,1,1-trifluoro acetone with NaNaph yielded a trace amount of the corresponding dimeric product.

The substrates used and the products obtained from treatment of various aromatic heterocycles with NaNaph are shown in Table 1. Trifluoroacetyl benzene (entry 6) gave the best yield of dimer (98%), but for benzotriazole (entry 4) a comparatively low yield (46%) was obtained. All the products were characterized by extensive NMR studies. The NMR data of three representative compounds are listed.[14]

Probably, the electron-withdrawing character of the fluorine atoms decreases the electron density of the corresponding system to such an extent that the initial attack by NaNaph to the carbonyl system is facilitated. But for *N*-alkyl indoles (Scheme 2), the yields decrease extensively with increasing +I effect of the alkyl group,

Table 1. Products isolated from the reactions between sodium naphthalenide and aromatic trifluoroacetyl compounds via Scheme 1

Entry	Substrate	Product	Yield (%)
1			94[13]
2			82
3			69
4			46
5			95
6			98
7			93



Scheme 2.

Table 2. Products isolated from the reactions between sodium naphthalenide and 3-trifluoroacetyl (*N*-alkyl) indoles via Scheme 2

Entry	Substrate	Product	Yield (%)
1	**1a**	**2a**	94
2	**1b**	**2b**	53
3	**1c**	**2c**	31
4	**1d**	**2d**	9
5	**1e**	— (no reaction)	—

in the order *n*-Pr > Et > Me. However, for the *N*-butyl derivative, the reaction did not take place at all (Table 2).

An attempt was also made using trichloro- and tribromoacetyl derivatives of indole as substrates. In both cases, no reaction was observed. Although the electron-withdrawing capacity of chlorine is high, yet perhaps it fails to decrease the electron density of the system enough so that the attack of NaNaph to the carbonyl group does not take place.

It was reported earlier that defluorination could be performed by electrolytic reduction,[15] but the present study reveals that the aromatic trifluoroacetyl derivatives on treatment with sodium naphthalenide yield symmetrical defluorinated dimers as the sole products. The reactivity decreases with increase in electron density of the aromatic system as well as the electron-donating nature of the substituents present in the substrate.

Acknowledgements

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14. A deep green dilute solution of sodium naphthalenide was prepared at 0 °C by treating 1.01 g (0.043 mol) sodium with 4.08 g (0.032 mol) naphthalene in dry THF (50 ml) under dry nitrogen. To this, a solution of the substrate (0.02 mol) in 20 ml THF was added and the mixture stirred for 2 h at 0–5 °C. The reaction mixture was then poured into 100 ml citric acid–sodium acetate buffer (pH ~ 4.5) and extracted thrice with 25 ml distilled chloroform. The chloroform extract was washed successively with aqueous sodium bicarbonate solution and distilled water, dried over sodium sulfate (anhydrous) and finally in a rotary evaporator under reduced pressure to remove a trace amount of water. Column chromatography yielded the corresponding defluorinated dimeric product. 1,4-(3,3′-Diindolyl)-1,4-dioxobutane; mp 189 °C: IR (KBr) 3236, 1640, 1432, 749 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 14.22 (2H, s), 10.03 (2H, d, $J = 7.8$ Hz), 9.83 (2H, s), 8.70 (2H, d, $J = 8.0$ Hz), 8.43–8.55 (4H, m), 4.77 (4H, s); ^{13}C NMR (125 MHz, pyridine-d_5) δ 196.10, 139.23, 134.85, 128.19, 124.01, 123.65, 123.63, 119.22, 113.78, 35.67; EIMS (70 eV) *m*/*z* 318 (M^++2, 39%). 1,4-(3,3′-(*N*-ethyl)diindolyl)-1,4-dioxobutane; mp 216 °C: IR (KBr) 1648, 1437, 748 cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 9.63 (2H, d, $J = 7.4$ Hz), 9.07 (2H, s), 8.59 (2H, d, $J = 7.8$ Hz), 8.37–8.43 (4H, m), 4.42 (4H, s), 2.52 (4H, m), 1.02 (6H, t, $J = 2.1$ Hz); ^{13}C NMR (125 MHz, pyridine-d_5) δ 194.16, 136.29, 133.98, 125.15, 123.01, 122.85, 122.63, 120.76, 114.09, 41.90, 34.98, 15.09; EIMS (70 eV) *m*/*z* 373 (M^++1, 54%). 1,4-Diphenyl-1,4-dioxobutane; mp 171 °C: IR (KBr) 1680, 1575, 1480, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (4H, distorted d), 7.30 (2H, m), 7.21 (4H, m), 4.72 (2H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 195.17, 136.30, 132.08, 127.20, 126.64, 37.85; EIMS (70 eV) *m*/*z* 238 (M^+, 26%).
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