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Acylation of Activated Aromatic Substrates under Mild Conditions with $(RCO)_2O$/ Me_2S/BF_3

Alexander S. Kiselyov, Ronald G. Harvey*
Ben May Institute, The University of Chicago, Chicago, IL 60637

Abstract: An efficient procedure for acylation and perfluoroacylation of activated aromatic substrates under mild conditions using the system $(RCO)_2O/Me_2S/BF_3$ in CH_2Cl_2 is described. It is believed that dimethylacylsulfonium salts, $RCOSMe_2+ RCO_2BF_3-$, are the active acylating agents.

In connection with studies on the chemistry of polycyclic aromatic hydrocarbons (PAHs) and their oxidized metabolites,[1] we required a mild and reliable procedure for the acetylation and trifluoroacetylation of PAHs. While Friedel-Crafts acylation has been extensively investigated,[2] the standard Lewis acid catalysts, e.g. $AlCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$, and the vigorous reaction conditions usually employed were likely to be too strenuous for some of the more sensitive PAHs of interest. We now report application of the system $(RCO)_2O/Me_2S/BF_3$, previously utilized for the acylation of alkenes and alkynes,[3] to the acylation of various polycyclic aromatic molecules under mild conditions (Table 1).

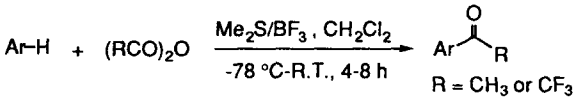
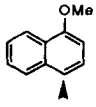
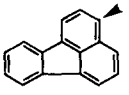
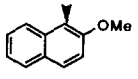
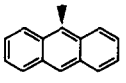
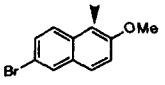
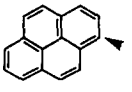
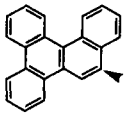


Table 1. Acetylation and trifluoroacetylation of PAHs using $(RCO)_2O/Me_2S/BF_3$.

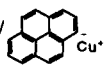
Run	Ar-H[a]	Yields,[b] %		Run	Ar-H	Yields,[b] %	
		R = CH_3	R = CF_3			R = CH_3	R = CF_3
1		76	67	5		59	56
2		74	70	6		62	58
3		69	63	7		88	71
4		78	76	8		64	56

[a] The principal site of substitution is indicated by an arrow. [b] Yields are for the pure isolated compounds.[4]

Acetylation and trifluoroacetylation of activated aromatic substrates using the system $(RCO)_2O/Me_2S/BF_3$, where R = CH_3 or CF_3, proceeded smoothly to provide monoacylated products in yields comparable to those found with conventional catalyst systems. Thus, various methoxynaphthalenes (Runs 1-3), *N*-methylindole (Run 4), and polyarenes containing three or more fused aromatic rings (Runs 5-8) underwent acetylation and trifluoroacetylation readily under the standard conditions employed.[5] These reactions were found to be highly efficient in that monoacetylated products were formed exclusively with essentially no concurrent formation of secondary products or tars. Moreover, substitution generally took place with high regioselectivity to yield a single isomer within the limits of experimental detection. On the other hand, the method was less satisfactory with unactivated aromatic substrates with fewer than three rings. Attempts to introduce acetoxy or trifluoracetoxy functions into anisole, naphthalene, 1-methyl-, and 1,4-dimethylnaphthalenes by this method under the conditions described were not successful. Fluorene and *m*-triphenylene also failed to react under these conditions. The best yields of the acylated products were achieved when the ratio of the reagents was: PAH substrate/$(RCO)_2O$/ Me_2S/BF_3 = 1:2:2:2. Lower ratios of PAH compound/acylating agent afforded lower yields of acylated products. However, increasing the PAH/acylating agent ratio had no effect on conversion of the starting compounds or product yields. Most satisfactory solvents were the chlorinated hydrocarbons CH_2Cl_2 and $ClCH_2CH_2Cl$ purified by predistillation over CaH_2.[3] Reactions conducted in benzene, fluorobenzene, or nitrobenzene resulted in slightly lower yields of acetylated products.

A comparison was conducted of the trifluoroacetylation of pyrene by the Me_2S/BF_3 reagent under the conditions utilized herein with the trifluoroacetylation of pyrene using various other Friedel-Crafts catalyst systems and procedures previously described in the literature. The results are presented in Table 2. The best

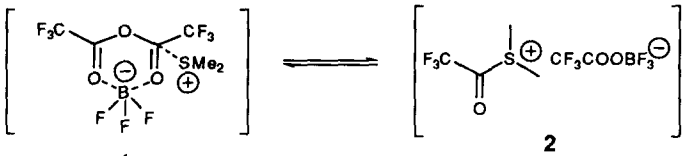
Table 2. Comparison of Reagents for the trifluoroacetylation of pyrene.

Run	Reagent System	Ratio Pyrene/Reagent	Conditions	Yield[a], %
1	$(CF_3CO)_2O/Me_2S/BF_3$	1 : 2	CH_2Cl_2, -78°C - R.T., 12 hrs.	71
2	$CF_3CO_2SO_2CF_3$	1 : 1.1	benzene, 80°C, 12 hrs.	77
3	$CF_3COCl/AlCl_3$	1 : 2[b]	CH_2Cl_2, -15°C - R.T., 12 hrs.	66
4	$CF_3COCl/AlBr_3$	1 : 2[b]	CH_2Cl_2, -15°C - R.T., 12 hrs.	59
5	$CF_3COCl/TiCl_4$	1 : 2[b]	CH_2Cl_2, -15°C - R.T., 12 hrs.	14[c]
6	$(CF_3CO)_2O/BF_3/Et_2O$	1 : 2[b]	CH_2Cl_2, -15°C - R.T., 12 hrs.	no rxn
7[d]	$(CF_3CO)_2O$/N base	1 : 2[b]	benzene, 80°C, 12 hrs.	no rxn
8	$(CF_3CO)_2O/$ 		THF, -78°C - R.T., 8 hrs.	38

[a]Isolated yields. [b]Higher ratios of pyrene/acylating agent did not change the outcome of reaction. [c]Unreacted pyrene (74%) was recovered from the reaction mixture. [d]Nitrogen bases employed were 2,6-di-*tert*-butyl-4-methylpyridine, 2,4,6-trimethylpyridine, and *N,N*-diisopropyl-*N*-ethylamine.

yield of trifluoromethyl pyrenyl ketone was obtained with trifluoroacetyl triflate (77%, Run 2).[6] The yield was only slightly lower (71%, Run 1) with the $(F_3CCO)_2O/Me_2S/BF_3$ system which has the advantage of being much less expensive. While reasonably satisfactory yields were found in reactions with F_3CCOCl/AlX_3 (66% and 59%, Runs, 3 and 4), tarry side products were also formed. These strong Lewis acids are likely to be poorly compatible with more sensitive functional groups. Similar reaction with $F_3CCOCl/TiCl_4$ was less satisfactory, providing the trifluoracetylated product in poor yield (14%, Run 5). Attempts to increase the yield by varying the PAH substrate/acylating reagent ratio or by refluxing the reaction mixture were not successful. The important role of Me_2S in the reactions involving the Me_2S/BF_3 complex is demonstrated by the fact that substitution of the Et_2O/BF_3 complex resulted in no reaction (Run 6). Attempts to trifluoroacetylate pyrene by reaction with $(F_3CCO)_2O$ and various nitrogen bases (2,4,6-trimethylpyridine, *N,N*-diisopropyl-*N*-ethylamine, 2,6-di-*tert*-butyl-4-methylpyridine) also failed to yield trifluoracetylated product (Run 7). Comparison was also made with the synthesis of trifluoromethyl pyrenyl ketone from the organocopper compound prepared from 1-bromopyrene.[7] However, the yield of 1-trifluoroacetoxypyrene via this route was only a moderate (38%, Run 8). In summary, the $(F_3CCO)_2O/Me_2S/BF_3$ reagent is a mild and efficient acylating agent, comparable in acylating power to trifluoroacetyl triflate. It appears to offer significant advantages of convenience and yield for the trifluoroacetylation of polycyclic aromatic molecules.

The nature of the active acylating species in the $(F_3CCO)_2O/Me_2S/BF_3$ system has been suggested to involve coordination of Me_2S with the carbonyl function of the anhydride to form an intermediate complex **1** that is in equilibrium with a sulfonium salt **2**.[3] Further experimental study will be required to determine the validity of this mechanism. In any case, this reagent appears to be potentially of broad general utility for the synthesis of trifluoromethyl aryl ketones.[8]



1 **2**

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4. Selected physical data (Run #, **a**, R = CH_3, **b**, R = CF_3): 1**a**: mp 72-74 °C (lit. 72-74 °C, Dixon, E. A.; Fischer, A.; Robinson, F. P. *Can. J. Chem.* **1981**, *59*, 2629); 2**a**: mp 104-105 °C (lit. 104-105 °C,

Leonard, N. J.; Hyson, A. M. *J. Am. Chem. Soc.* **1949**, *71*, 1392); **3a**: mp 60-62 °C; ^{1}H NMR (300 MHz) δ 2.82 (s, Me), 3.98 (s, 3, Me), 7.12 (d, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 7.64 (d, 1, *J* = 7.8 Hz), 7.73 (d, 1, *J* = 7.8 Hz), 7.80 (d, 1, *J* = 7.8 Hz); HR MS, Calcd. for $C_{13}H_{11}BrO_2$: 277.99429 (^{79}Br), 279.99224 (^{81}Br); Found: 277.99405 (^{79}Br), 279.99201 (^{81}Br); **4a**: mp 117-118 °C; (lit. 117-118 °C, Bergman, J. *Acta Chem. Scand.* **1968**, *22*, 1063); **5a**: mp 124-125 °C (lit. 128-129 °C, Campbell, N.; Easton, W. W. *J. Chem. Soc.* **1949**, 340.); ^{1}H NMR (500 MHz) δ 2.91 (s, Me), 7.37 (t, 1,*J* = 7.5 Hz), 7.41 (t, 1, *J* = 7.5 Hz), 7.68 (dd, 1,*J* = 7.5 Hz, *J* = 6.5 Hz), 7.85 (d, 1,*J* = 7.5 Hz), 7.88-7.94 (m, 2H), 8.17 (d, 1,*J* = 7.5 Hz), 8.73 (d, 1, *J* = 7.5 Hz). **6a**: mp 75-76 °C (lit. 75-76 °C, Beil. 7(2), 450); **7a**: mp 87-89 °C (lit. 86-89 °C, Beil. 7(3), 2726); **8a**: mp 180-182 °C; ^{1}H NMR (300 MHz) δ 2.98 (s, 3, Me), 7.54-7.84 (m, 8, Ar), 8.58 (d, 1,*J* = 7.5 Hz), 8.66 (t, 1, *J* = 7.8 Hz), 8.76 (t, 1, *J* = 7.8 Hz), 8.96 (s, 1, Ar); ^{13}C NMR (75 MHz) 29.78; 116.75; 119.88, 120.12, 120.52, 122.46, 122.48, 122.57, 123.28, 123.35, 124.30, 124.36, 124.62, 125.62, 125.67, 126.13, 126.24, 127.51, 129.73, 130.91, 131.15, 132.56, 134.45, 196.24. HR MS, Calcd. for $C_{24}H_{16}O$: 320.12012. Found: 320.12047; **1b**: mp 54-55 °C, ^{1}H NMR (300 MHz) δ 3.96 (s, Me), 6.62 (d, 2,*J* = 8.4 Hz), 7.52 (t, 1, *J* = 7.8 Hz), 7.68 (t, 1, *J* = 7.8 Hz), 8.18 (d, 1, *J* = 7.8 Hz), 8.27 (d, 1, J = 7.8 Hz); ^{13}C NMR (75 MHz) 56.15, 102.36, 118.15 (q, *J* = 288 Hz, CF_3), 119.23, 122.35, 126.11, 126.23, 126.36, 130.05, 133.22, 135.82, 162.18, 179.92 (q, *J* = 39 Hz, CO); HR MS, Calcd. for $C_{13}H_9F_3O_2$: 254.05546. Found: 254. 0.5560. **2b**: mp 66-67 °C, ^{1}H NMR (300 MHz) δ 4.02 (s, Me), 7.22 (d, 1, *J* = 7.8 Hz), 7.34 (t, 1, *J* = 7.8 Hz), 7.45 (t, 1, *J* = 7.8 Hz), 7.88-7.98 (m, 2H), 8.14 (d, 1, *J* = 7.8 Hz); ^{13}C NMR (75 MHz) 56.06, 103.15, 117.94 (q, *J* = 290 Hz, CF_3), 118.98, 122.25, 126.02, 126.19, 126.31, 128.44, 129.16, 138.73, 158.92, 180.06 (q, *J* = 38 Hz, CO); HR MS, Calcd. for $C_{13}H_9F_3O_2$: 254.05546. Found: 254.05470; **3b**: mp 85-87 °C, ^{1}H NMR (300 MHz) δ 4.02 (s, Me), 7.18 (d, 1, *J* = 7.8 Hz), 7.43 (s, 1H), 7.52 (d, 1, *J* = 7.8 Hz), 7.61 (d, 1, *J* = 7.8 Hz), 7.92 (d, 1, *J* = 7.8 Hz); ^{13}C NMR (75 MHz) 55.96, 103.56, 117.88 (q, *J* = 290 Hz, CF_3), 119.05, 122.12, 126.48, 126.54, 126.61, 130.11, 133.47, 136.02, 161.29, 180.13 (q, *J* = 38 Hz, CO); HR MS, Calcd for $C_{13}H_8BrF_3O_2$: 331.96598 (^{79}Br), 333.96393 (^{81}Br). Found: 331.96580 (^{79}Br), 333.96420 (^{81}Br); **4b**: mp 104-105 °C (lit. 105 °C, Whalley, W. B. *J. Chem. Soc.* **1954**, 1651); **5b**: mp 151-152 °C, ^{1}H NMR (500 MHz) δ 7.42 (t, 1,*J* = 7.5 Hz), 7.46 (t, 1, *J* = 7.5 Hz), 7.72 (dd, 1,*J* = 7.5 Hz, *J* = 6.5 Hz), 7.91 (d, 1,*J* = 7.5 Hz), 7.89-7.96 (m, 2H), 8.24 (d, 1,*J* = 7.5 Hz), 8.81 (d, 1, *J* = 7.5 Hz). HR MS, Calcd. for $C_{18}H_9F_3O$: 298.26703. Found: 298.26680; **6b**: m.p. 84-86 °C (lit. 84-86 °C, Forbus, T.R., Jr.; Martin, J.C. *J.Org.Chem.* **1979**, *44*, 313); **7b**: mp 126-128 °C, ^{1}H NMR (300 MHz) δ 7.56 (d, 1, *J* = 7.2 Hz), 7.73 (t, 1, *J* = 7.8 Hz), 7.75-7.83 (m, 5H), 8.18 (d, 1, *J* = 7.2 Hz), 8.91 (d, 1, *J* = 7.8 Hz); ^{13}C NMR (75 MHz) 116.98 (q, *J* = 292 Hz, CF_3), 120.54, 120.58, 120.62, 123.68, 123.74, 124.69, 125.81, 126.63, 127.06, 127.42, 128.23, 130.02, 130.58, 131.18, 135.61, 154.67, 181.02 (q, *J* = 39 Hz, CO), HR MS, Calcd. for $C_{18}H_9F_3O$: 298.06055. Found: 298.06120; **8b**: mp 192-194 °C, ^{1}H NMR (300 MHz) δ 7.60-7.91 (m, 8, Ar), 8.54 (d, 1, *J* = 7.5 Hz), 8.62 (t, 1, *J* = 7.8 Hz), 8.79 (t, 1, *J* = 7.8 Hz), 8.97 (d, 1, *J* = 7.8 Hz), 9.11 (s, 1, Ar). HR MS, Calcd. for $C_{24}H_{13}F_3O$: 374.09185. Found: 374.09207.

5. *Typical procedure*: A solution of 10 mM of freshly distilled anhydride in 2 mL of CH_2Cl_2 (predistilled over CaH_2) was added by syringe to a vigorously stirred solution of 10 mM of the Me_2S:BF_3 complex (Aldrich) in 10 mL of CH_2Cl_2 at -78 °C under argon. The mixture was stirred for 10 min, then a solution of 5 mM of the PAH substrate in 3 mL of CH_2Cl_2 was added by syringe, and the resulting solution was stirred at -78 °C for an additional 15 min. The solution was allowed to warm to room temperature (30 min), stirred for 12-24 h at this temperature, then poured into a mixture of saturated $NaHCO_3$ and CH_2Cl_2 and extracted with 3x20 mL of CH_2Cl_2. The extracts were combined, dried over Na_2SO_4, concentrated, and purified by chromatography on a column of Florisil eluted with hexanes/ether, 3:1 to give the pure products.

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