Diethylaminosulphur Trifluoride (DAST) as an Effective Reagent for Preparation of Methyl 2-Arylpropanoates from 1-Aryl-1,1-dimethoxypropan-2-ols

Takayoshi Yamauchi,* Kaneaki Hattori, Shun-ichi Ikeda, and Kentaro Tamaki
Sakai Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., 1-1-53, Takasu-cho, Sakai-shi, Osaka-fu 590, Japan

Treatment of dimethylacetals of aryl 1-hydroxyethyl ketones [$ArC(OMe)_2CH(OH)Me$] (Ar = Ph, 4-PhC_6H_4, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, 6-MeOnaphthalen-2-yl) with diethylaminosulphur trifluoride (DAST) affords smoothly the methyl 2-arylpropanoates in good yield *via* aryl-group migration. On the other hand, treatment of aryl 1-hydroxyethyl ketones with DAST gives the corresponding aryl 1-fluoroethyl ketones [ArCOCHFMe] (Ar = Ph, 4-PhC_6H_4, 4-$Bu^tC_6H_4$) in high yield.

Diethylaminosulphur trifluoride (DAST) has been developed as a selective fluorinating agent for the replacement of hydroxy groups or carbonyl oxygens with fluorine under very mild conditions,[1,2] and has found widespread utility in the fluorination of alcohols,[3–5] simple aldehydes, and ketones, dehydration of β-hydroxy-α-amino acids,[6] and the preparation of (α,α-difluoro)arylacetic acids from aryl keto esters.[7]

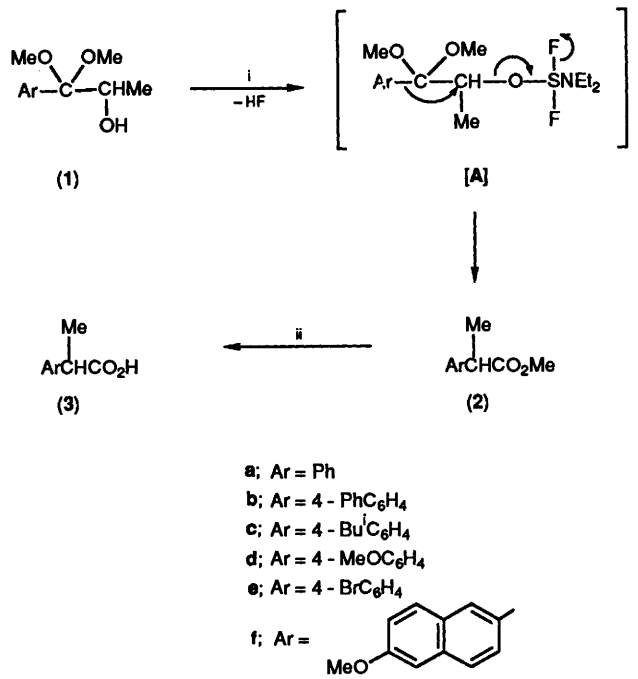
We report here a new application of DAST in synthetic organic chemistry. Recently, some of us disclosed a number of new and convenient preparative methods[8–13] for the synthesis of 2-arylpropanoic acids (**3**) from propiophenones and related substances, including a method of industrial manufacture.[8] It has been known that compounds (**3**) are useful medicinal drugs exhibiting non-steroidal anti-inflammatory activity.[14,15] We report here a new and readily occurring one-pot preparative method of esters of acids (**3**) from 1-aryl-1,1-dimethoxypropan-2-ols (**1**) and DAST *via* 1,2-aryl migration.[16]

Results and Discussion

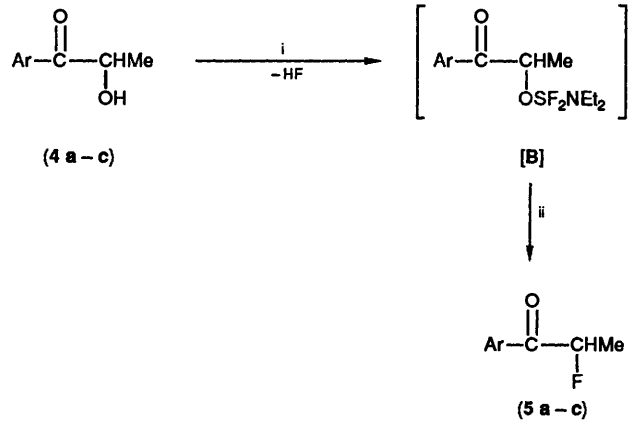
The reaction was generally carried out by addition of DAST to a dichloromethane solution of a 1-aryl-1,1-dimethoxypropan-2-ol (**1**) at 0–4 °C, the solution then being stirred for 1–2.5 h at 25 °C. The major product was the corresponding methyl 2-arylpropanoate (**2**) which were formed *via* 1,2-migration of the aryl group, and its alkaline hydrolysis afforded the corresponding acid (**3**) (Scheme 1).

Typical results are summarized in Table 1. The yield of the rearranged product was generally high when an electron-releasing group such as isobutyl, methoxy, or phenyl was present on a phenyl ring as substituent as in the case of the recently reported[8] SO_2Cl_2–weak-base-mediated preparation of esters (**2**) from alcohols (**1**). The reagent DAST was also revealed to be more effective than SO_2Cl_2–base, since even when the substituent group was an electron-attracting group such as bromine the yield of ester (**2**) was quite high.

DAST has been known as a selective fluorinating agent. As expected, the reaction of aryl 1-hydroxyethyl ketones (**4**) with DAST afforded the corresponding fluoro compounds (**5**) in high yield (Scheme 2 and Table 2). The formation of completely different compounds in Schemes 1 and 2 can be attributed to the difference in the aryl-group migratory attitude in intermediates [**A**] and [**B**]. In [**A**], aryl group migration occurs readily to give esters (**2**), while in [**B**] the aryl group on a carbonyl moiety cannot migrate and an S_N2 attack of fluoride ion prevails to afford fluoro ketones (**5**).[17]



Scheme 1. *Reagents:* i, DAST; ii, aq. NaOH, then aq. HCl.



Scheme 2. *Reagent:* i, DAST; ii, F^-.

Table 1. Rearrangement of 1-aryl-1,1-dimethoxypropan-2-ols (**1**).[a]

Compound (1)	DAST (mol equiv.)	Solvent	React. time (h)	Isolated yield of (2) (%)
a	2.0	CH_2Cl_2	2	74
b	2.0	CH_2Cl_2	1	92
c	2.0	CH_2Cl_2	1	94
c	2.0	Pyridine	1	85
d	2.0	Ch_2Cl_2	1	98
e	2.0	CH_2Cl_2	1	74
f	3.3	CH_2Cl_2	2.5	84

[a] (**1**) (2 mmol), solvent (10 ml), reaction temperature 25 °C.

Table 2. Reaction of aryl 1-hydroxyethyl ketones (**4**) with DAST.[a]

Compound (4)	Isolated yield of product (**5**) (%)
a	80 oil
b	83 m.p. 74–75 °C
c	99 oil

[a] (**4**) (2 mmol), solvent: CH_2Cl_2 (10 ml), reaction temperature 25 °C.

Experimental

^1H NMR spectra were recorded with a JEOL FX-90Q (90 MHz) instrument for solutions in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were recorded with a Hitachi M-80B instrument using electron impact (EI) at 70 eV. For chemical ionization (CI), isobutane was used as ionizing gas. M.p.s were determined with a Yanagimoto MP micro melting point apparatus and were uncorrected.

All starting organic and inorganic materials such as 2-halogenopropiophenones and DAST were commercial products of the purest grade. Several starting materials and products were identified by comparison of physical and spectroscopic data (IR and ^1H NMR) with the compounds obtained so far in our laboratory or prepared by known methods.[9,10,13]

1-Aryl-1,1-dimethoxypropan-2-ols (**1**).—Compounds (**1**) were prepared by the literature method[18] from methanol, sodium methoxide, and 2-halogenopropiophenones. 1,1-Dimethoxy-1-(6-methoxynaphthalen-2-yl)propan-2-ol (**1f**) was also prepared by the literature method.[19]

Rearrangement of 1-Aryl-1,1-dimethoxypropan-2-ols (**1**) *to Methyl 2-Arylpropanoates* (**2**).—A typical example is as follows. DAST (645 mg, 4 mmol) was added dropwise to a solution of 1-(4-isobutylphenyl)-1,1-dimethoxypropan-2-ol (**1c**) (504 mg, 2 mmol) in dichloromethane (10 ml) at 0–4 °C and then the mixture was stirred at 25 °C for 1 h. The resulting solution was treated with brine and extracted with chloroform (2 × 20 ml). The extract was dried ($MgSO_4$), and the solvent was evaporated off under reduced pressure. The resulting oily residue was purified by column chromatography on SiO_2 [hexane–ethyl acetate (30:1) as eluant] to give methyl 2-(4-isobutylphenyl)-propanoate (**2c**)[9] (416 mg, 94%) as an oil.

Preparation of Aryl 1-Hydroxyethyl Ketones (**4**).—A typical experimental procedure is as follows. A mixture of 1-(biphenyl-4-yl)-1,1-dimethoxypropan-2-ol (**1b**) (2.72 g, 10 mmol), toluene-*p*-sulphonic acid monohydrate (190 mg, 1 mmol), acetone (10 ml), and water (2 ml) was heated under reflux for 1.5 h. The solvent was evaporated off under reduced pressure. Dilute aq. sodium hydrogen carbonate (25 ml) and chloroform (30 ml) were added to the residue and the mixture was shaken. The organic layer was separated and the solvent was evaporated off under reduced pressure to give *biphenyl-4-yl 1-hydroxyethyl ketone* (**4b**) (2.25 g, 99%), m.p. 96–97 °C (from chloroform–hexane) (Found: C, 79.6; H, 6.2. $C_{15}H_{14}O_2$ requires C, 79.62; H, 6.24%); δ_H 1.48 (3 H, d, *J* 7 Hz, Me), 3.82 (1 H, br s, OH), 5.17 (1 H, q, *J* 7 Hz, CH), and 7.34–8.10 (9 H, m, ArH); *m/z* (EI) 226 (M^+, 6%), 181 (100), and 152 (34).

1-Hydroxyethyl 4'-isobutylphenyl ketone (**4c**) was similarly prepared: oil (Found: C, 75.3; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.8%); δ_H 0.91 (6 H, d, *J* 7 Hz, Me_2C), 1.45 (3 H, d, *J* 7 Hz, Me), 1.86 (1 H, m, CH), 2.54 (2 H, d, *J* 7 Hz, CH_2Ar), 3.80 (1 H, br s, OH), 5.12 (1 H, q, *J* 7 Hz, CHCO), 7.25 (2 H, d, *J* 9 Hz, ArH), and 7.83 (2 H, d, *J* 9 Hz, ArH); *m/z* (CI) 207 MH^+, 100%); *m/z* (EI) 161 (100%), 91 (17), and 43 (10).

Reaction of Aryl 1-Hydroxyethyl Ketones (**4**) *with DAST.*—A typical experimental procedure is as follows. DAST (484 mg, 3.0 mmol) was added dropwise to a solution of biphenyl-4-yl 1-hydroxyethyl ketone (**4b**) (452 mg, 2.0 mmol) in dichloromethane (10 ml) at 0–4 °C, and then the solution was stirred at 25 °C for 1 h. Dichloromethane (20 ml) and water (10 ml) were added to the mixture, which was then shaken. The organic layer was separated, and evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 [hexane–ethyl acetate (10:1) as eluant] to give *biphenyl-4-yl 1-fluoroethyl ketone* (**5b**) (378 mg, 83%), m.p. 74–75 °C (Found: C, 79.0; H, 5.8. $C_{15}H_{13}FO$ requires C, 78.93; H, 5.74%); δ_H 1.70 (3 H, dd, *J* 7 and 23 Hz, Me), 5.73 (1 H, dq, *J* 7 and 48 Hz, CHF), and 7.3–8.1 (9 H, m, ArH); *m/z* (EI) 208 (M^+, 1%), 161 (100), and 91 (15).

Similarly prepared were 1-fluoroethyl phenyl ketone[20] (**5a**) (243 mg, 80%), oil (Found: C, 70.8; H, 5.95. Calc. for C_4H_9FO: C, 71.04; H, 5.96%); δ_H 1.66 (3 H, dd, *J* 7 and 23 Hz, Me), 5.72 (1 H, dq, *J* 7 and 48 Hz, CHF), and 7.3–8.1 (5 H, m, Ph); *m/z* (EI) 152 (M^+, 5%), 105 (100), 77 (72), and 51 (34).

1-Fluoroethyl 4-isobutylphenyl ketone (**5c**) (414 mg, 99%), oil (Found: C, 74.85; H, 8.2. $C_{13}H_{17}FO$ requires C, 74.97; H, 8.23%); δ_H 0.91 (6 H, d, *J* 7 Hz, Me_2C), 1.64 (3 H, dd, *J* 7 and 23 Hz, Me), 1.86 (1 H, m, CH), 2.54 (2 H, d, *J* 7 Hz, CH_2Ar), 5.68 (1 H, dq, *J* 7 and 48 Hz, CHF), 7.23 (2 H, d, *J* 9 Hz, ArH), and 7.89 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI) 208 (M^+, 1%), 161 (100), and 91 (15).

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