Facile Synthesis of Bicyclo Orthoesters and Bicyclo Amide Acetals Using α,α-Difluoroalkylamines

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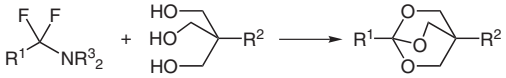
Abstract: Bicyclo orthoesters and amide acetals were prepared from the corresponding triols or diethanolamines using α,α-difluoroalkylamines. The reaction proceeded under milder conditions than conventional methods. 4-*tert*-Butyl-1-(4-ethynylphenyl)trioxabicyclo[2.2.2]octane, a new class of insecticide, was prepared from a triol in three steps using a difluoroalkylamine.

Key words: bicyclo orthoesters, bicyclo amide acetals, α,α-difluoroalkylamines, protecting groups, polymers

Bicyclo orthoesters have been used by organic chemists as a protecting group for carboxylic acids,[1] however, they have recently attracted the attention of a wide range of chemists because bicyclo orthoesters, such as 1,4-disubstituted 2,4,6-trioxabicyclo[2.2.2]octanes, have been found to be a highly potent insecticide.[2] Moreover, it was found that bicyclo orthoesters polymerize reversibly to offer an environmentally-friendly recycling system for polymeric materials.[3] The bicyclo orthoesters were prepared by transetherification from the corresponding trialkyl orthocarboxylates and triols, however, the reaction is reversible and requires high temperature over a long period to obtain the products.[4] The bicyclo orthoesters were also prepared by acid-catalyzed isomerization of the carboxylate esters of hydroxymethyloxetanes,[1,5] however, in this case, harsh reaction conditions are required for the preparation of the starting hydroxymethyloxetanes.[5] Therefore, more facile and convenient methods are required for the synthesis of bicyclo orthoesters.

Recently, we found that the reaction of α,α-difluoroalkylamines with 2-aminoalcohols, 2-aminothiols, and 1,3-diamines proceeds rapidly to give five-membered heterocyclic compounds under mild conditions.[6] During the course of the study, we found that the reaction of the difluoroalkylamines with triols proceeds quickly to give bicyclo orthoesters under mild conditions (Equation 1).

Various difluoroalkylamines can be prepared from the corresponding carboxylic amides in two steps.[6] When 1,1,1-tris(hydroxymethyl)ethane (**1**) was allowed to react with *N*,*N*-diethyl-α,α-difluorobenzylamine (DFBA) in DMF, the reaction went to completion at room temperature in two hours to give 4-methyl-1-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (**5**) in 66% yield (Table 1). Under the same conditions, the *tert*-butyl-substituted bicyclo orthoester **6** was obtained from **1** in 70% yield with *N*-(1,1-difluoro-2,2-dimethylpropyl)pyrrolidine instead of DFBA. On the other hand, the benzoyloxy-substituted triol **2**, which is less soluble in DMF, did not react to completion with DFBA under the same conditions. When the reaction was performed in deuterated chloroform and followed by NMR, the reaction was found to be complete in one hour at 50 °C; the corresponding bicyclo orthoester **7** was obtained in 62% yield. The bis-bicyclo orthoester of dipentaerythritol **3** was previously prepared by transetherification using triethyl orthopropionate. The reaction was performed at high temperature (180–200 °C) for six hours, and the desired bifunctional bicyclo orthoester was obtained in only 1.4% yield.[4c] On the other hand, the reaction of **3** with DFBA was complete in one hour at 60 °C, and the bis-bicyclo orthoester of benzoate **8** was obtained in 96% yield. Difluoroalkylamines can be used for the synthesis of cyclic amide acetals through reaction with diethanolamine **4**.[7] The reaction of *N*,*N*-diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA) with **4** was complete in 30 minutes at room temperature, and the resulting cyclic amide acetal **9** was isolated in 79% yield by distillation.



Equation 1

4-*tert*-Butyl-1-(4-ethynylphenyl)trioxabicyclo[2.2.2]octane (**13**) is a highly potent insecticide among the bicyclo orthobenzoate derivatives and was previously prepared from a hydroxymethyloxetane in four steps.[2b] It can be prepared more readily from 2-*tert*-butyl-2-hydroxymethylpropane-1,3-diol (**11**)[8] in three steps. Thus, preparation of a key intermediate, 1-(4-bromophenyl)-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane (**12**), was achieved in 79% yield from **11** by reaction with *N*,*N*-diethtyl-α,α-difluoro-4-bromobenzylamine at room temperature in two hours. Target **13** was prepared from **12** in 71% yield by a Sonogashira coupling reaction with trimethylsilylacetylene, followed by desilylation (Scheme 1).

Although difluoroalkylamines have been used for deoxyfluorination of alcohols, fluorination products were not formed under the conditions used (reaction temperature <70 °C).[9] The reaction must be proceeding through a cy-

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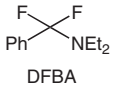
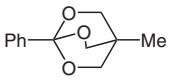
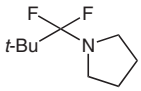
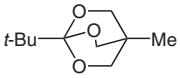
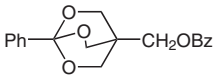
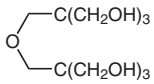
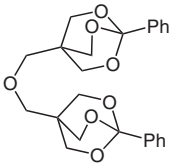
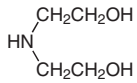
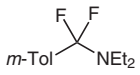
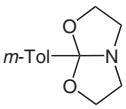
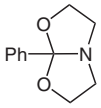
Table 1 Reaction of α,α-Difluoroalkylamines with Di- and Triols

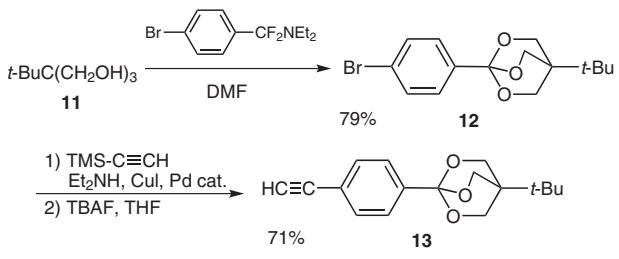
Substrate	$RCF_2NR'_2$	Solvent	Time (h)	Temp (°C)	Product	Yield (%)[a]
$MeC(CH_2OH)_3$ **1**	 DFBA	DMF	2	r.t.	 **5**	66
1		DMF	2	r.t.	 **6**	70
$BzOCH_2C(CH_2OH)_3$ **2**	DFBA	$CDCl_3$	1	50	 **7**	62
 **3**	DFBA	DMF	1	60	 **8**	96
 **4**	 DFMBA	CH_2Cl_2	0.5	r.t.	 **9**	79[b]
4	DFBA	$CDCl_3$	0.5	40	 **10**	64[b]

[a] Isolated yield based on substrate used.
[b] Isolated yield based on difluoroalkylamine used.

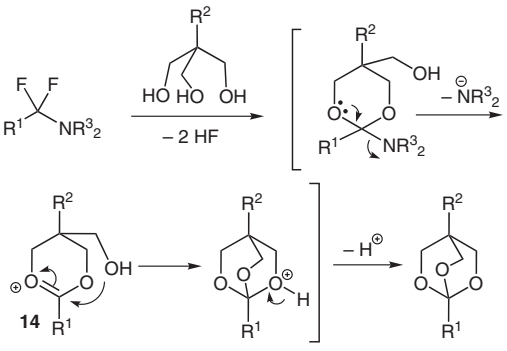
clic intermediate **14**, as in the reaction with 1,2- or 1,3-diols.[10] If a fluoride attacked the oxygen-attached carbon of **14**, a deoxyfluorination reaction would take place to give the fluorination product. However, due to the low nucleophilicity of the fluoride ion, attack of the free hydroxy group in **14** preceded the fluoride attack, to give the bicyclo orthoester (Scheme 2). Since all steps other than the fluoride attack are fast, the bicyclo orthoesters were formed under mild conditions.

In conclusion, a facile synthesis of bicyclo orthoesters and amide acetals from the corresponding triols or diethanolamine using α,α-difluoroalkylamines has been shown. The reaction was complete within two hours at room temperature to 60 °C and the products were obtained in good yields. Compared with the conventional methods, the reaction conditions are very mild and therefore, the present reaction is useful for the synthesis of various bicyclo orthoesters or amide acetals.

IR spectra were recorded using a JASCO FT/IR-410 spectrophotometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR spectrometer and chemical shifts (δ) are referred to TMS. The low and high-resolution mass spectra (EI) were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110 spectrometer. Small-scale distillations were carried out using a SIBATA glass tube oven



Scheme 1



Scheme 2

GTO-350RD. Polyols **1**, **3** and diethanolamine **4** were purchased from Tokyo Chemical Industry Co., Ltd. Triol **2** was prepared by mono-benzoylation of pentaerythritol obtained from Tokyo Chemical Industry Co., Ltd. 2-*tert*-Butyl-2-hydroxymethylpropane-1,3-diol (**11**) was prepared according to the literature.[8] Activated aluminum oxide (200 mesh) was obtained from Wako Pure Chemicals Industries, LTD. Difluoroalkylamines were prepared from the corresponding carboxylic amides according to the literature.[6]

***N*,*N*-Diethyl-α,α-difluorobenzylamine (DFBA)**
Bp 42–45 °C (0.1 mmHg).

^{1}H NMR ($CDCl_3$): δ = 7.62–7.59 (m, 2 H), 7.43–7.40 (m, 3 H), 2.90 (q, *J* = 10.5 Hz, 4 H), 1.06 (t, *J* = 10.5 Hz, 6 H).

***N*,*N*-Diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA)**
Bp 84–88 °C (5 mmHg).

^{1}H NMR ($CDCl_3$): δ = 7.41–7.17 (m, 4 H), 2.92 (q, *J* = 7.0 Hz, 4 H), 2.39 (s, 3 H), 1.07 (t, *J* = 7.1 Hz, 6 H).

***N*-(1,1-Difluoro-2,2-dimethylpropyl)pyrrolidine**
Bp 51 °C (7 mmHg).

^{1}H NMR ($CDCl_3$): δ = 3.07–3.03 (m, 4 H), 1.80–1.76 (m, 4 H), 1.13 (s, 9 H).

***N*,*N*-Diethyl-α,α-difluoro-4-bromobenzylamine**
Bp 62–64 °C (0.1 mmHg).

^{1}H NMR ($CDCl_3$): δ = 7.55 (d, *J* = 8.5 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 2.85 (q, *J* = 7.1 Hz, 4 H), 1.04 (t, *J* = 7.2 Hz, 6 H).

4-Methyl-1-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (5); Typical Procedure
A mixture of **1** (180 mg, 1.5 mmol) and powdered MS (4 Å; 300 mg) in anhyd DMF (3 mL) was stirred at r.t. for 1 h. The mixture was cooled to 0 °C and DFBA (199 mg, 1 mmol) was added. After stirring at r.t. for 2 h, the mixture was poured into sat. aq $NaHCO_3$ (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (activated alumina; hexane–Et_2O, 1:1) gave **5**.

Yield: 136 mg (66%); white solid; mp 125–126 °C (Lit.[11] 128–129 °C).

IR (KBr): 2881, 1337, 996 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.63–7.61 (m, 2 H), 7.35–7.34 (m, 3 H), 4.10 (s, 6 H), 0.89 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 137.4, 129.1, 128.0 (2 × C), 125.6 (2 × C), 107.4, 73.2 (3 × C), 30.5, 14.5.

1-*tert*-Butyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (6)
Product was isolated by column chromatography (activated alumina; hexane–Et_2O, 1:1).

White sold; mp 94–95 °C (Lit.[12] 102 °C).

IR (KBr): 2881, 1337, 996 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 6 H), 0.96 (s, 9 H), 0.78 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 111.9, 72.6 (3 × C), 37.3, 30.1, 24.8 (3 × C), 14.5.

4-Benzoyloxymethyl-1-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (7)
A mixture of **2** (240 mg, 1 mmol) and DFBA (199 mg, 1.5 mmol) in $CDCl_3$ (5 mL) was stirred at 50 °C for 1 h (consumption of **2** was confirmed from ^{1}H NMR analysis). The mixture was poured into sat. aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The product was isolated by column chromatography (activated alumina; hexane–CH_2Cl_2, 1:1).

Yield: 202 mg (62%); white solid; mp 117–118 °C.

IR (KBr): 2950, 2889, 1735, 1338, 1101 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.03 (d, *J* = 7.0 Hz, 2 H), 7.65–7.60 (m, 3 H), 7.50–7.46 (m, 2 H), 7.37–7.36 (m, 3 H), 4.31 (s, 6 H), 4.21 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 165.9, 137.0, 133.6, 129.6 (2 × C), 129.3, 129.1, 128.6 (2 × C), 128.0 (2 × C), 125.6 (2 × C), 108.0, 69.7 (3 × C), 62.4, 34.9.

HRMS (FAB): *m*/*z* [M + 1] calcd for $C_{19}H_{19}O_5$: 327.1232; found: 327.1231.

1-Phenyl-4-{[(1-phenyl-2,6,7-trioxabicyclo[2.2.2]octane-4-yl)methoxy]methyl}-2,6,7-trioxabicyclo[2.2.2]octane (8)
A mixture of **3** (254 mg, 1 mmol) and DFBA (796 mg, 4 mmol) in anhydrous DMF (1 mL) was stirred at 60 °C for 1 h. The mixture was poured into sat. aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization from CH_2Cl_2–hexane gave the pure product.

Yield: 409 mg (96%); white solid; mp 210 °C.

IR (KBr): 2883, 1339, 1088 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.63–7.61 (m, 4 H), 7.37–7.35 (m, 6 H), 4.19 (s, 12 H), 3.27 (s, 4 H).

^{13}C NMR ($CDCl_3$): δ = 137.1 (2 × C), 129.3 (2 × C), 128.0 (4 × C), 125.6 (4 × C), 107.9 (2 × C), 70.2 (2 × C), 69.8 (6 × C), 35.4 (2 × C).

HRMS (FAB): *m*/*z* [M + 1] calcd for $C_{24}H_{27}O_7$: 427.1757; found: 427.1758.

5-(3-Methylphenyl)-1-aza-4,6-dioxabicyclo[3.3.0]octane (9)
To a solution of **4** (788 mg, 7.5 mmol) in CH_2Cl_2 (3 mL), was added DFMBA (1.07 g, 5 mmol) at 0 °C, and the mixture was stirred at r.t. for 30 min. The mixture was poured into sat. aq $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by Kugelrohr distillation to give **9**.

Yield: 810 mg (79%); bp 120 °C (bath temperature) / 0.1 mmHg.

IR (neat): 2882, 1631, 1471, 1300, 1080 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.43–7.41 (m, 1 H), 7.27–7.21 (m, 2 H), 7.14–7.12 (m, 1 H), 4.17–4.09 (m, 2 H), 4.05–3.94 (m, 2 H), 3.43–3.33 (m, 2 H), 3.15–3.07 (m, 2 H), 2.63 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 14.00, 137.7, 129.2, 127.9, 126.5, 123.2, 122.9, 65.6 (2 × C), 53.0 (2 × C), 21.4.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1104.

5-Phenyl-1-aza-4,6-dioxabicyclo[3.3.0]octane (10)
Bp 95 °C (bath temperature)/0.1 mmHg (Lit.[7a] 79–80 °C/0.03 mmHg).

IR (neat): 2883, 1626, 1448, 1281, 1067 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.62–7.60 (m, 2 H), 7.34–7.28 (m, 3 H), 4.13–4.08 (m, 2 H), 4.01–3.96 (m, 2 H), 3.38–3.33 (m, 2 H), 3.11–3.05 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 140.2, 128.3, 128.0, 125.9 (2 × C), 123.2 (2 × C), 65.6 (2 × C), 53.0 (2 × C).

1-(4-Bromophenyl)-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane (12)
The reaction was carried out as described for **5**, to give **12**, which was isolated by column chromatography (activated alumina; hexane–CH_2Cl_2, 1:1).

Yield: 258 mg (79%); white solid; mp 177 °C.

IR (KBr): 2962, 1340, 1008, 820 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.47 (s, 4 H), 4.17 (s, 6 H), 0.91 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 136.6, 131.1 (2 × C), 127.5 (2 × C), 123.4, 107.2, 68.4 (3 × C), 38.4, 31.4, 25.2 (3 × C).

HRMS (FAB): *m/z* [M + 1] calcd for $C_{15}H_{20}BrO_3$: 327.0596; found: 327.0606.

4-*tert*-Butyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octane (13)

A mixture of **12** (262 mg, 0.8 mmol), trimethylsilylacetylene (393 mg, 4 mmol), $Pd(PPh_3)_2Cl_2$ (40 mg, 0.057 mmol), and CuI (3 mg, 0.015 mmol) in Et_3N (8 mL) was stirred under an N_2 atmosphere at 80 °C overnight (consumption of **12** was confirmed by GC). Volatile material was removed under reduced pressure and the residue was extracted with Et_2O (3 × 20 mL). The combined organic layer was concentrated under reduced pressure. and the residue was dissolved in THF (8 mL). A THF solution of TBAF (1 M, 1.2 mL, 1.2 mmol) was added and the mixture was stirred at r.t. for 1 h. The product was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (activated alumina; hexane–CH_2Cl_2, 1:1) gave **13**.

Yield: 154 mg (71% yield from **12**); white solid; mp 148–150 °C (Lit.[2b] 167–168 °C).

IR (KBr): 3265, 2962, 2892, 1344, 1130, 1009, 834 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.65 (d, *J* = 8.3 Hz, 2 H), 7.47 (d, *J* = 8.3 Hz, 2 H), 4.18 (s, 6 H), 3.07 (s, 1 H), 0.92 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 137.9, 131.8 (2 × C), 125.7 (2 × C), 122.8, 107.2, 83.4, 77.6, 68.4 (3 × C), 38.4, 31.4, 25.2 (3 × C).

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