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

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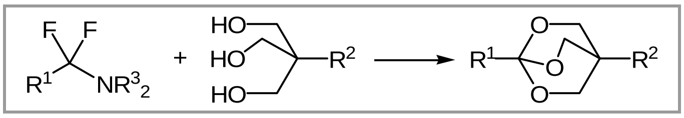
Abstract: Bicyclo orthoesters and amide acetals were prepared from the corresponding triols or diethanolamine using α,α-difluoroalkylamines. The reaction proceeds under milder conditions compared with the conventional methods. 4-*tert*-Butyl-1-(4-ethynylphenyl)trioxabicyclo[2.2.2]octane, a new class of insecticide, was prepared from a triol in 3 steps using a difluoroalkylamine.

Key words: bicyclo orthoesters, bicyclo amide acetals, α,α-difluoroalkylamines, protecting group, polymer

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 environment-friendly recycling system for polymer materials.[3] The bicyclo orthoesters were prepared by transetherification from the corresponding trialkyl orthocarboxylates and triols.[4] However, the reaction is reversible and is performed at 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, severe 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).

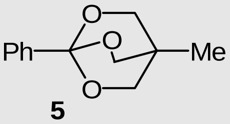
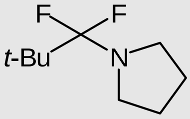
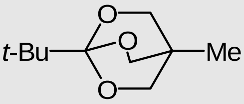
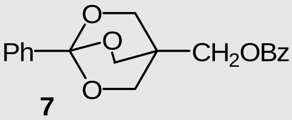
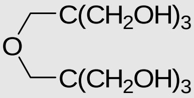
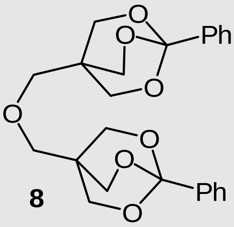
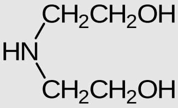
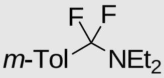
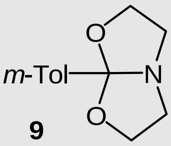
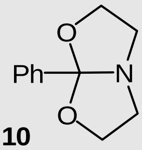
Various difluoroalkylamines can be prepared from the corresponding carboxylic amides in two steps.[6] When 1,1,1-tris(hydroxymethyl)ethane **1** was allowed to react with *N*,*N*-diethyl-α,α-difluorobenzylamine (DFBA) in DMF, the reaction was completed at r.t. in 2 h to give 4-methyl-1-phenyl-2,6,7-trioxabicyclo[2.2.2]octane **5** in 66% yield (Table 1). Under the same conditions, the *t*-butyl group 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, a benzoyloxy group substituted triol **2** is less soluble in DMF and its reaction with DFBA was not completed under the same conditions. Therefore, the reaction was performed in $CDCl_3$ and was followed by NMR. Consequently, the reaction was completed in 1 h at 50 °C and the corresponding bicyclo orthoester **7** was obtained in 62% yield. 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 6 h, 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 completed in 1 h 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 by the reaction with diethanolamine **4**.[7] The reaction of *N*,*N*-diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA) with **4** was completed in 0.5 h at r.t. and the resulting cyclic amide acetal **9** was isolated in 79% yield by distillation.



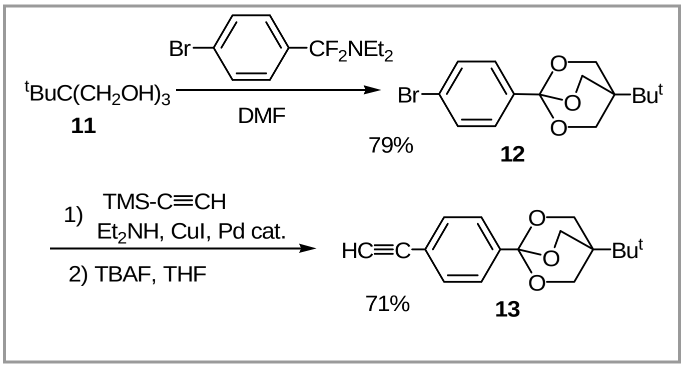
Equation 1

4-*tert*-Butyl-1-(4-ethynylphenyl)trioxabicyclo[2.2.2]octane **13** is a highly potent insecticide among 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 r.t. in 2 h. Target **13** was prepared from **12** with 71% yield by Sonogashira coupling reaction with trimethylsilylacetylene followed by desilylation (Scheme 1).

Table 1

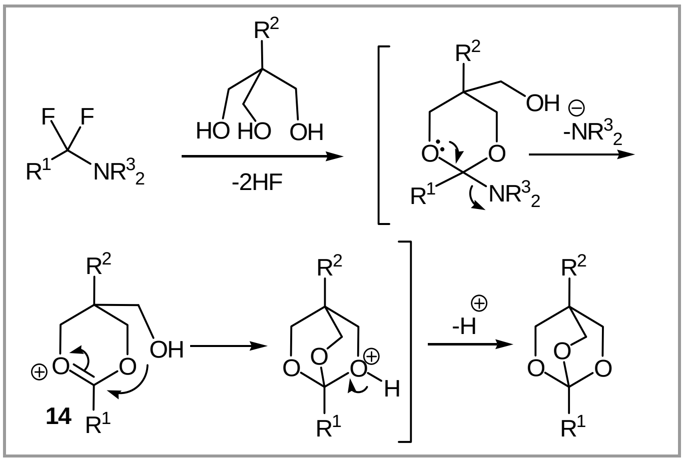
Substrate	$RCF_2NR'_2$	Solvent	Conditions	Product	Yield (%)
$MeC(CH_2OH)_3$ **1**	 DFBA	DMF	r.t. 2 h	 **5**	66[a]
1		DMF	r.t. 2 h	 **6**	70[a]
$BzOCH_2C(CH_2OH)_3$ **2**	DFBA	$CDCl_3$	50 °C 1 h	 **7**	62[a]
 **3**	DFBA	DMF	60 °C 1 h	 **8**	96[a]
 **4**		CH_2Cl_2	r.t. 0.5 h	 **9**	79[b]
4	DFBA	$CDCl_3$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

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



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 cyclic 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, the 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.



Scheme 2

IR spectra were recorded using a JASCO FT/IR-410 spectrophotometer. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR spectrometer and the chemical shift δ are referred to tetramethylsilane. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110 spectrometer. A small scale distillation was carried out using SIBATA glass tube oven GTO-350RD. Polyols **1**, **3**, and diethanolamine **4** were purchased from Tokyo Chemical Industry Co., Ltd. A 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 literatures.[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, 2H), 7.43–7.40 (m, 3H), 2.90 (q, J = 10.5 Hz, 4H), 1.06 (t, J = 10.5 Hz, 6H).

N,N-Diethyl-α,α-difluoro-3-methylbenzylamine (DFMBA)

bp 84–88 °C / 5 mmHg.

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

N-(1,1-Difluoro-2,2-dimethylpropyl)pyrrolidine

bp 51°C / 7 mmHg

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

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, 2H), 7.47 (d, J = 8.5 Hz, 2H), 2.85 (q, J = 7.1 Hz, 4H), 1.04 (t, J = 7.2 Hz, 6H).

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 4A (300 mg) in dry DMF (3 mL) was stirred at room temperature for 1 h. Then, 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 aq sat. $NaHCO_3$ (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 : ether = 1:1) gave **5** (136 mg) in 66% yield; 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, 2H), 7.35-7.34 (m, 3H), 4.10 (s, 6H), 0.89 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 137.4, 129.1, 128.0 (2C), 125.6 (2C), 107.4, 73.2 (3C), 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 : ether = 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, 6H), 0.96 (s, 9H), 0.78 (s, 3H).

^{13}C NMR ($CDCl_3$) δ 111.9, 72.6 (3C), 37.3, 30.1, 24.8 (3C), 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 aq sat. $NaHCO_3$ (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 in 62% yield by column chromatography (activated alumina / hexane : CH_2Cl_2 = 1:1); white solid, mp 117–118 °C.

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

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

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

HRMS (Fab): *m/z* calcd for $C_{19}H_{19}O_5$ (M+1): 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 dry DMF (1 mL) was stirred at 60 °C for 1 h. Then the mixture was poured into aq sat. $NaHCO_3$ (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 pure product in 96% yield; white solid, mp 210 °C.

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

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

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

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

5-(3-Methylphenyl)-1-aza-4,6-dioxabicyclo[3.3.0]ocatne (9)

To a CH_2Cl_2 solution (3 mL) of **4** (788 mg, 7.5 mmol) was added DFMBA (1.07 g, 5 mmol) at 0 °C, and the mixture was stirred at r.t. for 30 min. Then the mixture was poured into aq sat. $NaHCO_3$ (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 Kugelrohr distillation gave **9** (810 mg) in 79% yield; bp 120 °C (bath temperature) / 0.1 mHg.

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

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

^{13}C NMR ($CDCl_3$) δ 14.00, 137.7, 129.2, 127.9, 126.5, 123.2, 122.9, 65.6 (2C), 53.0 (2C), 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]ocatne (10)

bp 95 °C (bath temperature) / 0.1 mHg (Lit.[7a] 79–80 °C / 0.03 mHg).

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

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

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

1-(4-Bromophenyl)-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane (12)

The reaction was carried out as in the case of **5**, and **12** was isolated by column chromatography (activated alumina / hexane : CH_2Cl_2 = 1:1) in 79% yield; white solid; mp 177 °C.

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

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

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

HRMS (Fab): m/z calcd for $C_{15}H_{20}BrO_3$ (M+1): 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 N_2 atmosphere at 80 °C overnight. Consumption of **12** was confirmed by GC and volatile material was removed under reduced pressure. The residue was extracted with ether three timed and the combined organic layer was concentrated under reduced pressure. The residue was dissolved in THF (8 mL), and a THF solution of TBAF (1.2 mL of 1M solution, 1.2 mmol) was added. The mixture was stirred at r.t. for 1 h and the product was 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 : CH_2Cl_2 = 1:1) gave **13** (154 mg) in 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}.

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

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

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