1,3-Dipolar Cycloaddition of Difluoro(methylene)cyclopropanes with Nitrones: Efficient Synthesis of 3,3-Difluorinated Tetrahydropyridinols

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Abstract: Difluoro-substituted spirocyclopropaneisoxazolidines were formed by 1,3-dipolar cycloaddition of difluoro(methylene)cyclopropanes (F_2MCPs) with nitrones in high yields. The [3+2]-cycloaddition reactions exhibited good regioselectivity and high stereoselectivity. The cycloadducts could rearrange further to form highly substituted 3,3-difluorinated tetrahydropyridinols.

Key words: fluorine, difluoro(methylene)cyclopropanes, 3,3-difluorinated tetrahydropyridinols, ring rearrangement, 1,3-dipolar cycloaddition, nitrone

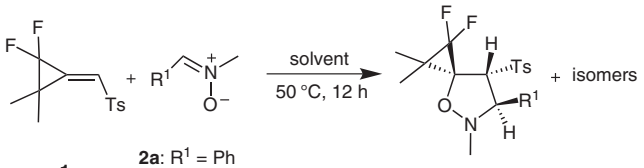
Methylenecyclopropane derivatives (MCPs), which are relatively stable but highly strained molecules, have attracted chemists' attention over the past decades.[1] With regard to the cycloaddition reaction of these compounds, there is a great deal of interest in the 1,3-dipolar cycloaddition of nitrones. In most cases, the corresponding 1,3-dipolar cycloadducts could rearrange further to form N-heterocyclic six-membered-ring compounds at high temperature, such as 4-pyridones or 4-pyridinols.[2] This synthetic methodology has been demonstrated as a useful strategy to synthesize azaheterocyclic skeletons,[3] which exist widely in natural products and pharmaceutical intermediates.[4]

It is well known that the incorporation of fluorine into organic molecules could have profound effects on their physical and biological properties.[5] For the purpose of exploiting new efficient bioactive structures, fluorine chemists made great efforts in synthesizing such fluorine-containing azaheterocyclic skeletons.[6] For example, Qing designed and synthesized several nojirimycin analogues (*gem*-4,4-difluorinated iminosugars). The biological evaluation of these azaheterocyclic structures revealed that the *gem*-difluoromethylene group generally reduced the inhibition of glycosidases.[7] However, multiple reaction steps are always required for the synthesis of these compounds.

Difluoro(methylene)cyclopropanes (F_2MCPs), the fluorinated analogues of MCPs, have been less studied over the past decades due to the difficulties in synthesis.[8] Recently, we disclosed a route to prepare sulfonyl difluoro(methylene)cyclopropanes (F_2MCPs) by the reaction of difluorocarbene with 1,2-allenic sulfones, and found that this kind of F_2MCP could react with cyclic dienes with high regio- and stereoselectivity.[9] Considering the importance of 1,3-dipolar cycloaddition of MCPs in the construction of azaheterocyclic skeletons and the bioactivity of the fluorinated analogues, we investigated the [3+2]-cycloaddition of F_2MCP with nitrones and found that a series of highly substituted *gem*-difluorinated tetrahydropyridinols could be readily prepared.

Treatment of F_2MCP **1** with phenyl-*N*-methylnitrone (**2a**) in toluene at 50 °C for eight hours in a sealed tube gave a good yield of **3a** (81%) together with a small amount of other isomers **3a′** (Table 1, entry 1). High yields of expected **3a** could be obtained in 1,4-dioxane with 2–3% inseparable isomers **3a′**, which was determined by ^{19}F NMR spectroscopy (entry 3). Fortunately, reaction in petroleum ether afforded **3a** as the only product in 95% yield (entry 7). In the case of 4-nitrophenyl-*N*-methylnitrone (**2b**), which does not dissolve well in nonpolar solvents, **3b** was formed as the sole cycloadduct when 1,4-dioxane was used as a co-solvent in petroleum ether (entry 8). The con-

Table 1 Optimization of the Reaction Conditions for the 1,3-Dipolar Cycloaddition



1 **2a**: R^1 = Ph; **2b**: R^1 = 4-$O_2NC_6H_4$ **3** **3'**

Entry	Nitrone	Solvent	Product	Yield (%)[a]	**3**:**3′**[b]
1	**2a**	toluene	**3a**	81	20:1
2	**2a**	[bmim][PF_6][c]	**3a**	51	20:1
3	**2a**	1,4-dioxane	**3a**	99	40:1
4	**2a**	Et_2O	**3a**	73	16:1
5	**2a**	MeCN	**3a**	73	11:1
6	**2a**	MeOH	**3a**	56	100:0
7	**2a**	PE	**3a**	95	100:0
8	**2b**	co-solvent[d]	**3b**	55	100:0

[a] Total yield of **3** and **3′**.
[b] Determined by ^{19}F NMR.
[c] 1-Butyl-3-methylimidazoliumhexafluorophosphate.
[d] PE–1,4-dioxane (2:1).

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figuration of **3b** was confirmed by ^{1}H NMR and 2D NOESY experiments. The proton H^a appeared at δ = 3.93 ppm as a doublet, and was coupled to proton H^b (J = 4.1 Hz), which indicated that the two protons were placed at the adjacent carbon atoms (Figure 1). Although NOE effects of H^a–H^c, H^a–H^d, H^b–H^d, and H^b–H^c were unambiguously detected, there was no observable correlation between H^d and H^c in its 2D NOESY spectrum, which indicated that the tosyl group is situated *anti* to the 4-nitrophenyl group.

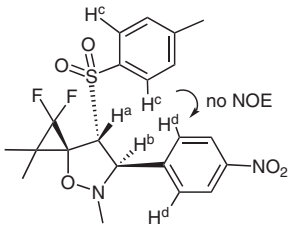
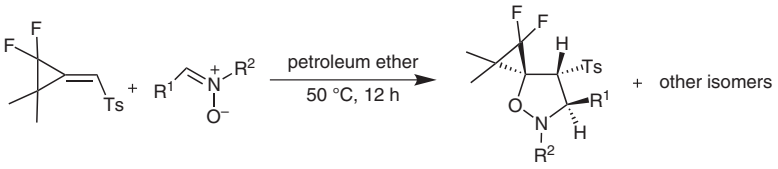


Figure 1 Configuration of **3b**

With the optimized reaction conditions in hand, we extended the [3+2] cycloaddition to other nitrones. All aryl-substituted *N*-methylnitrones **2c**–**2g** reacted smoothly with **1** to give the corresponding difluorinated spirocyclopropaneisoxazolidines in moderate to good yields (Table 2). As for the more polar nitrones like **2f**, a small portion of 1,4-dioxane should also be added to facilitate the solubilization (entry 4). Small amounts of isomers (2–3%) were still found in the case of **2d** and **2e** with a halogen on the benzene ring (entries 2 and 3). As for the alkyl- or alkenyl-substituted nitrones **2h** and **2i**, higher amounts of isomers (5% and 12%) were observed and the efforts to obtain pure products failed (entries 6 and 7). Changing the substituents on the nitrogen atom from methyl to phenyl or isopropyl resulted in no reaction (entries 8 and 9), which demonstrated that the steric hindrance of the substituents on the nitrogen had a significant effect on the reactivity.

Thermal rearrangement of the difluoro-substituted spirocyclopropaneisoxazolidines was then investigated. When **3a** was heated in *tert*-butanol at 100 °C in a sealed tube for four hours, the signals of **3a** (δ = –144.9, –158.2 ppm; J = 151 Hz) in ^{19}F NMR disappeared and a new AB peak signal appeared at δ = –109.9 and –125.6 ppm with a coupling constant of 269 Hz, indicating the opening of the difluorocyclopropane ring. After column chromatography and recrystallization in $CHCl_3$, **4a** was obtained in 40% yield and its structure was confirmed by single crystal X-ray analysis.[11] As shown in Figure 2, a tetrahydropyridinol structure was formed. Due to the presence of the adjacent strong electron-withdrawing CF_2 and tosyl groups, the 4-carbonyl group in **4a** adopts the enol form. The thermal instability of the cycloadducts **3** encouraged us to try a one-pot procedure for the synthesis of difluorinated tetrahydropyridinols. Treatment of nitrone **2a** with 1.02–1.05 equivalents of **1** in petroleum ether at 100 °C for eight hours afforded **4a** in nearly quantitative yield as determined by ^{19}F NMR (Table 3). Further investigation revealed that this enol structure decomposed upon column

Table 2 Reaction of F_2MCP **1** with Nitrones[10]



1 **2c–k** **3c–k** **3'**

Entry	Nitrone	R^1	R^2	**3** (%)[a]	**3′** (%)
1	**2c**	4-MeOC$_6$H$_4$	Me	**3c**, 63	–[b]
2	**2d**	4-BrC$_6$H$_4$	Me	**3d**, 75	3
3	**2e**	4-ClC$_6$H$_4$	Me	**3e**, 85	2
4	**2f**	4-HOC$_6$H$_4$	Me	**3f**, 90[c]	–[b]
5	**2g**	1-naphthyl-C$_6$H$_4$	Me	**3g**, 87	–[b]
6	**2h**	PhCH=CH	Me	**3h**, 80[d]	5
7	**2i**	*i*-Pr	Me	**3i**, 69[d]	12
8	**2j**	Ph	Ph	**3j**, –[e]	–[b]
9	**2k**	Ph	*i*-Pr	**3k**, –[e]	–[b]

[a] Isolated yield.
[b] No isomers were formed.
[c] 1,4-Dioxane was used as co-solvent.
[d] The crude yield was determined by ^{19}F NMR.
[e] No reaction was observed.

chromatography. Pure crystals of **4** could be obtained in moderate to high yields after precipitation, filtration and recrystallization. It should be noted that *N*-phenylnitrone **2j**, which did not afford the cycloadduct **3j** at 50 °C (Table 2, entry 8) reacted well with **1** at 65 °C within six hours to give **4j** in one step (Table 3, entry 7). The cycloadduct **3j** was never detected by ^{19}F NMR during the reaction process, which indicated that **3j** was not as stable as other adducts and would rearrange immediately. The mechanism of the rearrangement was considered to be a diradical process as proposed initially by Brandi.[2] Cycloadduct **3a** was chosen as the model compound to illustrate the process (Scheme 1). The cleavage of N–O bond occurred upon heating to give a diradical intermediate **5**, followed by ring opening to form a new diradical **6**, which cyclized readily into the difluorinated tetrahydropyridinol **4a**.[11]

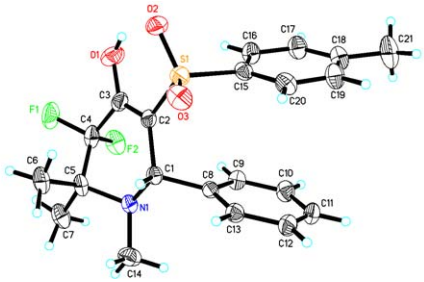
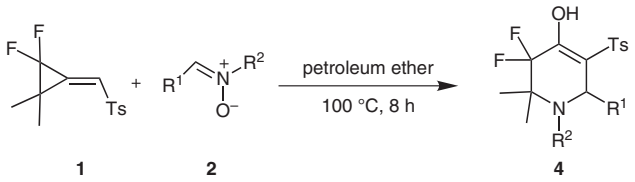


Figure 2 Crystal structure of **4a**

Table 3 One-Pot Synthesis of Pyridinol Compounds **4**[12]

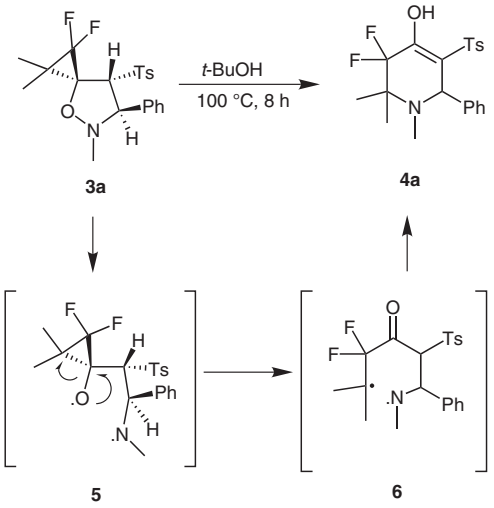


1 **2** **4**

Entry	Nitrone	R^1	R^2	**4** (%)[a]
1	**2a**	Ph	Me	**4a** (70)
2	**2b**	4-$O_2NC_6H_4$	Me	**4b** (79)
3	**2c**	4-$MeOC_6H_4$	Me	**4c** (82)
4	**2d**	4-BrC_6H_4	Me	**4d** (75)
5	**2e**	4-ClC_6H_4	Me	**4e** (69)
6	**2h**	PhCH=CH	Me	**4h** (70)
7	**2j**	Ph	Ph	**4j** (58)[b]

[a] Isolated yield.
[b] Reaction performed in 1,4-dioxane at 65 °C.

In summary, we have developed an efficient one-pot procedure for the synthesis of 3,3′-difluorinated tetrahydropyridinols by combining the 1,3-dipolar cycloaddition of F_2MCPs and nitrones with subsequent rearrangement of the corresponding adducts. It seems likely that a number of difluorinated azaheterocycles could be synthesized by this method from readily available starting materials.



3a **4a**

5 **6**

Scheme 1 Thermal rearrangement of **3a**

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **Preparation of 1,1-Difluoro-2,2,5-trimethyl-6-phenyl-7-tosyl-4-oxa-5-azaspiro[2.4]heptane (3a)**: Into a 5-mL sealed tube were added **1** (50 mg, 0.184 mmol), phenyl-*N*-methylnitrone (**2a**; 30 mg, 0.22 mmol) and PE (1.5 mL). The mixture was stirred at 50 °C for 12 h. After cooling to r.t., the solvent was removed under reduced pressure. The residue was purified by chromatography on a silica gel column (PE–EtOAc, 10:1) to yield **3a** as a viscous oil (70 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.53 (s, 3 H), 2.48 (s, 3 H), 2.55 (s, 3 H), 3.89 (d, *J* = 4.8 Hz, 1 H), 4.06 (d, *J* = 4.8 Hz, 1 H), 6.91–6.97 (m, 2 H), 7.15–7.25 (m, 3 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.2 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –144.9 (d, *J* = 151 Hz, 1 F), 158.2 (d, *J* = 151 Hz, 1 F). IR (film): 3066, 3035, 3008, 2969, 2933, 2878, 1597, 1496, 1479, 1457, 1436, 1325, 1305, 1249, 1209, 1188, 1149, 1125, 1087, 1078 cm^{-1}. MS (ESI): *m*/*z* = 430.0 [M + Na$^+$]. Anal. Calcd for $C_{21}H_{23}F_2NO_3S$: C, 61.90; H, 5.69; N, 3.44. Found: C, 61.87; H, 5.80; N, 3.05.

(11) The single-crystal X-ray structural data for **4a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 684886.

(12) **Preparation of 3,3-Difluoro-1,2,2-trimethyl-6-phenyl-5-tosyl-1,2,3,6-tetrahydropyridin-4-ol (4a)**: Into a 5-mL sealed tube were added **1** (50 mg, 0.184 mmol), phenyl-*N*-methylnitrone (**2a**; 24 mg, 0.184 mmol) and PE (2.5 mL). The mixture was stirred at 100 °C for 8 h. After cooling to r.t., 3,3-difluoro-1,2,2-trimethyl-6-phenyl-5-tosyl-1,2,3,6-tetrahydropyridin-4-ol (**4a**) was precipitated. After removing the solvent by filtration, the residue was recrystallized in $CHCl_3$ by slow evaporation. Yield: 52 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.30 (s, 3 H), 1.93 (s, 3 H), 2.32 (s, 3 H), 4.11 (d, *J* = 9.8 Hz, 1 H), 6.87–7.01 (m, 9 H), 10.6 (s, 1 H). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –109.0 (dd, *J* = 9.7, 269 Hz, 1 F), –125.6 (d, *J* = 269 Hz, 1 F). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 20.2 (d, J_{FC} = 4 Hz), 21.4, 32.1, 59.0 (dd, J_{FC} = 15, 18 Hz), 62.7, 113.9 (m), 115.4 (t, J_{FC} = 184 Hz), 126.3, 127.7, 127.9, 129.4, 130.3, 137.8, 138.3 (d, J_{FC} = 2 Hz), 143.8, 152.3 (t, J_{FC} = 19 Hz). IR (film): 3235, 2995, 2821, 1643, 1598, 1496, 1456, 1369, 1317, 1289, 1276, 1249, 1217, 1175, 1148, 1125, 1101, 1070, 1057, 1017, 994 cm^{-1}. MS (ESI): *m*/*z* = 408.1 [M + H$^+$].