An Improved Method for Difluorocyclopropanation of Alkenes

Duncan M. Gill,[a] Neil McLay,[a] Michael J. Waring,[b] Christopher T. Wilkinson,[a] Joseph B. Sweeney*[a]

[a] Department of Chemical Sciences, University of Huddersfield, Queensgate, Huddersfield, West Yorkshire, HD1 3DH, UK

[b] Oncology Innovative Medicines, AstraZeneca PLC, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TF, UK
E-mail: j.b.sweeney@hud.ac.uk

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Abstract: Difluorocyclopropanation of alkenes using fluorinated acetate salts using convential heating is often a slow, inefficient, and energy-intensive process. We report here a modified protocol which enables the rapid (<5 min) preparation of 1,1-difluorocyclopropanes, using microwave irradiation. The new procedure is not only considerably faster than previously reported methods, but it also employs easily removed, low boiling-point solvents and avoids the use of highly toxic or ozone-depleting substances.

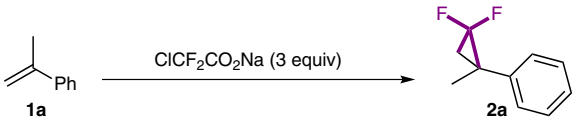
Key words: difluorocyclopropane, cyclopropanation, microwave, pharmacophore, greener

Since replacement of C–H bonds by C–F bonds is a key strategy in drug design,[1] direct access to fluorinated cyclopropanes is a valuable synthetic method, and since the first report of the generation and addition of difluorocarbene to cyclohexene[2] there has been continued interest[3] in processes which can efficiently deliver the 1,1-difluorocyclopropyl motif.[4] Small-ring synthesis using carbenes and their equivalents is exemplified in the cyclopropanation of alkenes, for which a range of reagents and procedures have been reported. The reaction has both chemical and biological impact, since the privileged nature of the cyclopropyl motif predicates its inclusion in many synthetic bioactive compounds,[5] including a wide range of active drug substances.

Amongst the methods commonly in use, thermal decomposition of halodifluoroacetate salts have received particular attention; thus, chloro- and bromodifluoracetates can both be used for (1,1-difluoro)cyclopropanation of alkenes, but the reported protocols typically require large excesses of reagents, high temperatures, high-boiling solvents, and/or long reaction times. There are other reagents which can be used as precursors to the highly electron-deficient difluorocarbene species, but there remain complications, such as the use of high boiling solvents,[6] non-trivial precursor synthesis, the use of ozone-depleting substances[7] or toxic heavy metals.[8] Thus the development of practical new methods for difluorocyclopropanation of alkenes continues to attract researchers. We report here a rapid, practical procedure for difluorocyclopropanation of alkenes using microwave irradiation, in THF solution.

Our study began with an examination of the reaction of sodium chlorodifluoroacetate in the presence of 2-phenylpropene (**1a**) under microwave irradiation over a range of power levels and temperatures, giving difluorocyclopropane (**2a**).[2,9,10] It quickly transpired that 300 W was the optimum power level required to initiate the reaction (Table 1); under these conditions the cyclopropanation reaction was complete within five minutes, which represents a significant truncation in reaction time compared to other methods. A key drawback to reported procedures using fluoroacetates is the requirement for high-boiling solvents; in all of the reactions we carried out THF was used as solvent, greatly facilitating subsequent product processing.

Table 1 Reaction Conditions Screen



1a 2a

Entry	Power (W)	Temp (°C)	Time (min)	Conversion (%)[a]
1	300	170	15	100
2	300	150	15	99
3	300	130	15	33
4	300	170	10	100
5	300	170	5	100
6	200	157	15	100
7	100	153	15	84
8	300	170	5	9[b]
9	300	170	5	61[c]

[a] Conversion calculated by NMR spectroscopy.
[b] Conditions: 1 mol equiv of sodium chlorodifluoroacetate.
[c] Conditions: 2 mol equiv of sodium chlorodifluoroacetate.

The cyclopropanes in each instance were routinely extracted into diethyl ether following aqueous workup, and in most instances the crude product was then simply purified by column chromatography on silica with hexane. Armed with a robust method, we proceeded to an examination of the scope of the procedure.

As shown in Table 2, a range of alkenes undergo difluorocyclopropanation,[11] with excellent conversions and in good yields. The limiting factor in the reaction is the vol-

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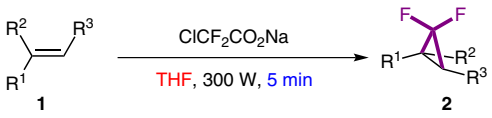
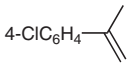
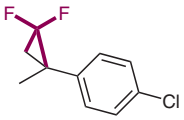
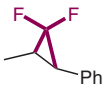
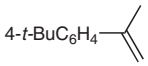
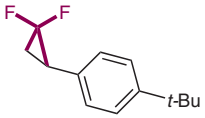
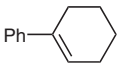
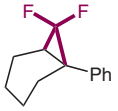
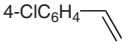
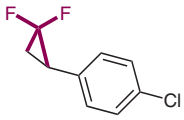
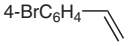
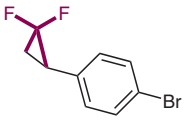
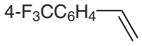
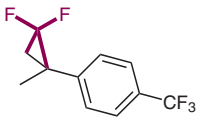
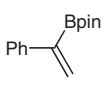
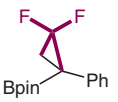
atility of the difluorinated products, which can compromise isolation; in all of the examples given, isolated yields were generally very good and NMR analysis showed essentially quantitative conversions in the majority of reactions.

Table 2 Substrate Screen



Entry	Olefin **1**		Cyclopropane **2**		Conversion (%)[a]	Isolated yield (%)
1	**1a**		**2a**		99	75
2	**1b**		**2b**		100	87
3	**1c**		**2c**		99	87
4	**1d**		**2d**		100	78
5	**1e**		**2e**		97	76
6	**1f**		**2f**		99	75
7	**1g**		**2g**		100	75
8	**1h**		**2h**		99	72
9	**1i**		**2i**		99	71
10	**1j**		**2j**		95	67
11	**1k**		**2k**		99	42
12[b]	**1l**		**2l**		100	70

[a] Calculated using NMR spectroscopy.
[b] Bpin = tetramethyldioxaborolane.

In conclusion, we have developed a highly practical microwave-mediated procedure for the addition of difluorocarbene to olefins. The method offers greatly reduced reaction times, employs easily removed, low-boiling solvents, and uses an accessible and cost-effective non-ozone-depleting substance as a difluorocarbene source. We believe this combination of desirable characteristics will prove of utility.

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(10) **Data for 2a**
Clear colorless oil (269.5 mg, 75%); R_f = 0.30 (100% hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (5 H, m), 1.71–1.66 (1 H, m), 1.52 (3 H, dd, *J* = 3.0, 2.0 Hz), 1.43–1.40 (1 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 128.5, 128.3, 127.2, 114.5, 31.2, 22.5, 21.4. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –132.3 to –132.7 (1 F, m), –137.3 to –137.7 (1 F, m). IR: ν_{max} = 2981, 1500, 1469, 1445, 1369, 1300, 1208.9, 1172, 1097, 1065, 1006, 932, 902, 869, 765, 716, 610, 545, 480 cm^{-1}. MS: *m/z* calcd for $C_{10}H_{10}F_2$: 168.0751; found: 168.9; *m/z* calcd for $C_9H_7F_2$ = 153.0506; found: 153.1.
(11) **Typical Experimental Procedure**
Sodium chlorodifluoroacetate (914 mg 6.0 mmol) was completely dissolved in a THF solution (4.0 mL) of alkene (2.0 mmol) and exposed to MW irradiation (using a Milestone MicroSYNTH reactor and Q20 vessel with Weflon® button and magnetic stirring bead). Twist control, rotor control, start parameters, and continuous power were all selected. T2 control was used with 89% stirring. Method parameters were set at 300 W, 170 °C, 00:05:00). After sampling for quantitative NMR studies, the reaction mixture was diluted with H_2O (20.0 mL) and the crude reaction product extracted into Et_2O (3 × 20.0 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to yield the crude product as a brown oil. The crude reaction products were purified by column chromatography using 100% hexanes as eluent.

