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Synthesis of difluorosubstituted six-membered nitronates via an addition/substitution cascade

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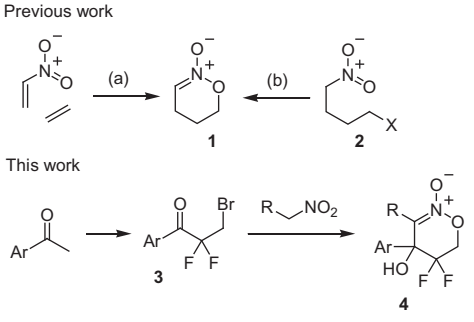
ABSTRACT

A method for the synthesis of 5,5-difluorosubstituted six-membered nitronates by the coupling of 2-bromo-1,1-difluoroethyl ketones with nitro alkanes is described. The reaction is mediated by 1,8-diazabicycloundec-7-ene and proceeds as a sequence of nitronate anion addition at the carbonyl group and intramolecular nucleophilic substitution of bromine.

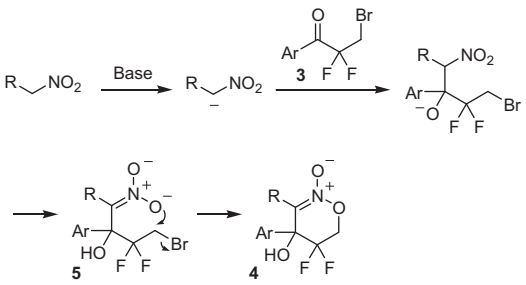
Six-membered nitronates **1** (5,6-dihydro-4*H*-1,2-oxazine *N*-oxides) represent a valuable class of compounds for synthetic organic chemistry, due to their versatile reactivity which includes 1,3-dipolar cycloaddition, nucleophilic addition at the C=N bond, and reductive tranformations.[1,2] As a result, they have found applications as intermediates for the synthesis of natural products[1a,3] and medicinal agents.[1b,4]

Nitronates **1** can be accessed either by [4+2] cycloaddition (path a)[1a] or by intramolecular nucleophilic substitution (path b).[1c] The former approach is straightforward, but is only applicable to the synthesis of a limited class of nitronates. In the second method, the synthesis of suitable starting nitro compounds **2** bearing a leaving group may be difficult (see Scheme 1).



Scheme 1. Synthesis of six-membered nitronates.

While many nitronates have been synthesized,[1,5] nitronates **1** containing a fluorine atom in the ring have not been described. At the same time, introduction of fluorine may affect the chemical and biological properties of organic molecules.[6] Herein, we report a convenient method for the synthesis of *gem*-difluorinated six-membered nitronates **4** (Scheme 2) from difluorinated ketones **3** which were prepared in one step from widely available ketones using a brominative difluorohomologation reaction recently reported by our group.[7]



Scheme 2. Formation of nitronates **4**.

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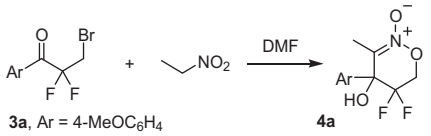
Table 1
Optimization studies



3a, Ar = 4-MeOC$_6$H$_4$ 4a

Entry	$EtNO_2$ (equiv)	Base (equiv)	Conditions	Conversion of **3a**[a] (%)	Yield of **4a**[a] (%)
1	1.4	K_2CO_3 (2)	rt, 30 min	<5	Traces
2	1.4	K_2CO_3 (2)	rt, 18 h	100	59
3[b]	1.2	*t*-BuOK (1.3)	−20 °C to rt, then rt, 18 h	55	41
4	1.5	DBU (2.5)	rt, 2 h	100	77
5	1.2	DBU (1.4)	rt, 1 h	89	76
6	1.7	DBU (2)	−10 °C to rt, then rt, 1 h	100	86 (85[c])

[a] Determined by ^{19}F NMR of the reaction mixture.
[b] DMF/THF (1:1).
[c] Isolated yield.

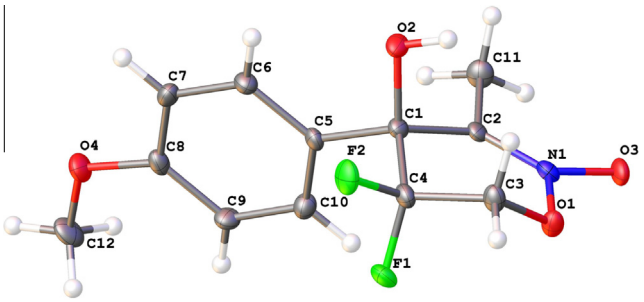
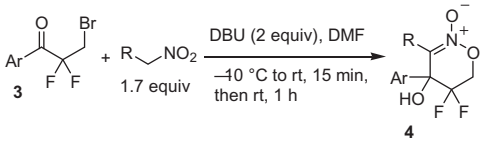


Figure 1. Single crystal X-ray structure of nitronate **4a**.

Ketones **3** were previously demonstrated to behave as efficient 1,3-dielectrophiles in reactions with phenylhydrazine.[7a] In the present work, nitro compounds were employed as formal 1,3-dinucleophiles in coupling reactions with ketones **3**. Thus, deprotonation of the nitro compound generates a nitronate anion, which attacks at the carbonyl group. Subsequent shift of hydrogen from the nitro group to the alkoxide provides anion **5** which is capable of intramolecular substitution of bromine.

Ketone **3a**, derived from 4-methoxyacetophenone, was selected as a model substrate and its reaction with nitroethane evaluated (Table 1). When potassium carbonate in dimethylformamide was used, the reaction proceeded slowly, and complete conversion of ketone **3a** was achieved after 18 h (entries 1 and 2). However, product **4a** turned out to be base-sensitive, and degraded upon

Table 2
Synthesis of nitronates **4**



3 4

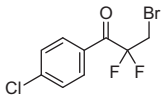
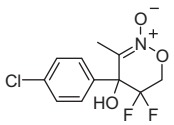
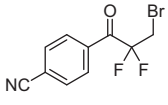
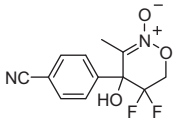
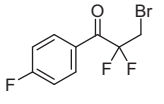
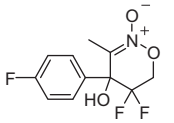
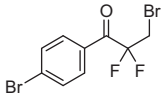
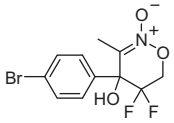
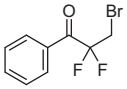
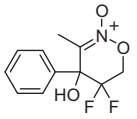
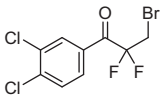
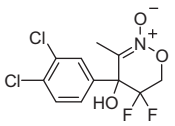
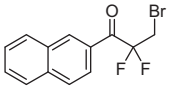
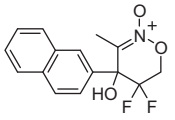
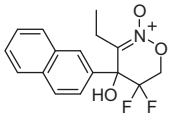
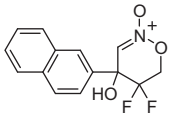
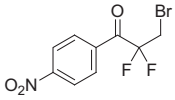
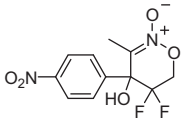
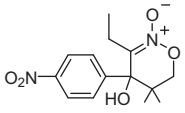
Entry	Ketone		R	Product		Yield of **4**[a] (%)
1		**3b**	Me		**4b**	77
2		**3c**	Me		**4c**	76
3		**3d**	Me		**4d**	85
4		**3e**	Me		**4e**	74

Table 2 (*continued*)

Entry	Ketone		R	Product		Yield of **4**[a] (%)
5	 **3f**	**3f**	Me	 **4f**	**4f**	78
6	 **3g**	**3g**	Me	 **4g**	**4g**	75
7	 **3h**	**3h**	Me	 **4h**	**4h**	80
8[b]		**3h**	Et	 **4i**	**4i**	56
9[b]		**3h**	H	 **4j**	**4j**	58
10	 **3i**	**3i**	Me	 **4k**	**4k**	91
11[b]		**3i**	Et	 **4l**	**4l**	56

[a] Isolated yield.
[b] HMPA.

prolonged stirring. 1,8-Diazabicycloundec-7-ene (DBU) was found to be the base of choice for this coupling.[8] The reaction with 2 equiv of DBU was complete within 1 h at room temperature, with the product **4a** formed in 86% yield according to ^{19}F NMR analysis. Due to the sensitivity of nitronate **4a** toward basic media, care should be taken upon work-up. For example, work-up with water and subsequent isolation afforded **4a** in only 50% yield. To prevent the decomposition of the nitronate, phosphate buffer (pH 6.5) was used for the work-up, thereby leading to **4a** in an isolated yield of 85%. The structure of nitronate **4a** was proved by single crystal X-ray analysis[9] (Fig. 1).

Under the optimized conditions, a series of ketones **3** were coupled with nitro compounds in typically good isolated yields (Table 2). However, substrates **3** bearing a substituent (methyl or chlorine) at the *ortho*-position gave slow reactions, presumably, owing to steric reasons. Reactions of ketones **3h**,**i** with nitromethane and nitropropane led to decreased yields under the standard conditions. Fortunately, switching to a more polar solvent, hexamethylphosphoramide (HMPA), allowed isolation of the expected nitronates **4i**,**j**,**l** in good yields (entries 8, 9, and 11).

In summary, a convenient protocol for the synthesis of 5,5-difluorosubstituted six-membered nitronates is described.[10] The reaction involves the base mediated coupling of nitroalkanes with difluorinated bromoketones. Since the latter substrates are obtained from methyl ketones, the target *gem*-difluorinated nitronates can be accessed from readily available starting materials in two steps.

Acknowledgement

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Supplementary data

Supplementary data (product characterization, NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.135.

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8. In the chemistry of aliphatic nitro compounds, DBU is frequently used for the generation of nitronate anions, see: (a) Aizpurua, J. M.; Oiarbide, M.; Palomo, C. *Tetrahedron Lett.* **1987**, *28*, 5361–5364; (b) Dilman, A. D.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Synthesis* **1999**, *1999*, 1767–1775; (c) Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.* **2002**, *43*, 5233–5235.
9. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1477091) and are available free of charge at CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ca.uk).
10. Synthesis of nitronates **4** (General procedure): Under an argon atmosphere, the reaction vessel was charged with ketone **3** (0.5 mmol, 1 equiv), nitro alkane (0.85 mmol, 1.7 equiv) and solvent (0.5 mL DMF for **4a**–**h**,**k**; HMPA for **4i**,**j**,**l**). The mixture was cooled to −10 °C and DBU (152 mg, 1 mmol, 2 equiv) was introduced through the septum. The reaction mixture was slowly warmed to room temperature over 15 min, and the solution stirred for an additional one hour. The mixture was quenched with a phosphate buffer (10 mL, 1 M, pH = 6.5), and aqueous phase extracted with ethyl acetate (3 × 4 mL). The combined organic layers were filtered through Na_2SO_4, the solvent evaporated under reduced pressure, and the residue purified by column chromatography on silica gel.