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# Generation and Intramolecular Cyclization of Difluoroalkyl Radicals *via* Single Electron Transfer from the Benzeneselenolate Anion: Synthesis of α,α-Difluoro-γ-lactams

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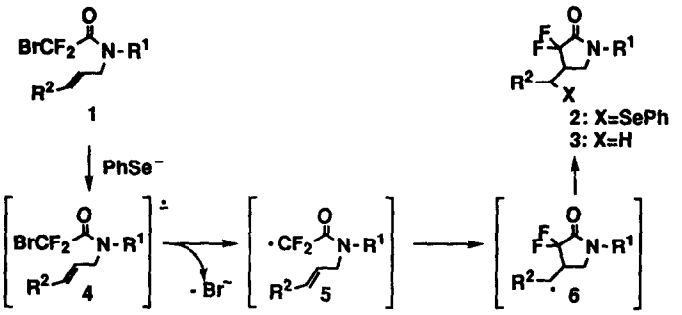
**Abstract:** Several α,α-difluoro-γ-lactams (2) were prepared by radical cyclization of amides (1) which were initiated by a single electron transfer (SET) process from the benzeneselenolate anion. Deselenation of these lactams (2) gave the corresponding α,α-difluoro-β-exomethylene lactams (3). © 1997 Elsevier Science Ltd.

Introduction of a difluoromethylene moiety into organic compounds often induces novel biological activities which are not found in the corresponding non-fluorinated compounds.[1] Because of the potential biological activity of some lactams, those including a difluoromethylene moiety are very attractive compounds but have been never synthesized.[2] Carbon-carbon bond formation *via* intramolecular cyclization is a common route to 5- and 6-membered rings.[3] However, there are few reports on cyclization of the α-fluorinated carbon radicals.[4] Barth et al. reported that α-iodoacetamide gave the 5-membered lactam in 60 % yield under the standard atom transfer cyclization reaction, but the corresponding α-fluoro-α-iodoacetamide gave only 13 % yield.[5] This result suggests that the α-fluorine atom of the acetamide group makes the cyclization more difficult. Itoh et al. also demonstrated successful radical cyclization of acetals derived from bromodifluoroacetaldehydes, but their attempts for radical cyclization of the corresponding esters were unsuccessful.[6]

Benzeneselenolate anion is a promising reducing reagent, because it is easily generated from diphenyl diselenide $(PhSe)_2$ by reduction and can be used as an excellent single electron transfer reducing agent.[7] Here, we describe the first synthesis of α,α-difluoro-γ-lactams (2) by the intramolecular seleno-alkylation of difluoroacetamide radicals (5) derived from *N*,*N*-substituted α,α-difluoroacetamides (1) (Scheme 1).



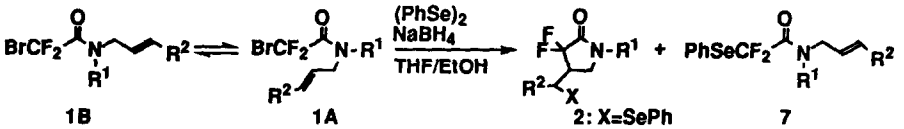

Scheme 1

The typical reaction was carried out under the following conditions: To a solution of $(PhSe)_2$ (0.15 mmol), $NaBH_4$ (0.30 mmol) and bromodifluoroacetamide (1) (0.30 mmol) in THF (8 ml) was added EtOH (2 ml) at 0 ℃. The reaction mixture was stirred for the 3 h at the same temperature under nitrogen atmosphere. After extraction, the crude product was purified by silica gel column chromatography to give 5-membered lactams (2) along with a by-product (7) (Table 1).

It is proposed that the conformation of the starting material is important in the radical cyclization.[8] Owing to restricted rotation around the carbonyl carbon-nitrogen bond, the starting amides consist of two rotamers. In fact, $^{19}F$ NMR of unsymmetrical amides (1) at room temperature shows two singlet signals for the fluorine atoms of the difluoromethylene unit attributed to the corresponding two rotamers. Rotamer 1A readily undergoes the intramolecular cyclization to the

lactam (2), while rotamer 1B preferentially undergoes intermolecular coupling to product (7) rather than intramolecular cyclization. So symmetrical amides were found to be suitable substrates for the reaction. Interestingly, both *N*-cinnamyl (entries 4 and 5) and crotyl compounds (entry 6) provided the deselenated compounds (3).

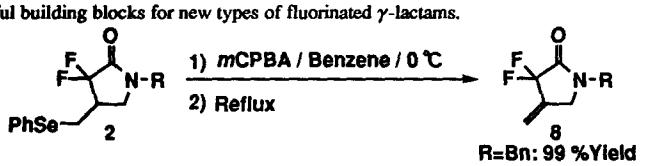
**Table 1 Synthesis of α,α-Difuluoro-γ-lactams *via* Radical Cyclization of 1**




| Entry | $R^1$ | $R^2$ | Yield (%) | | |
|---|---|---|---|---|---|
| | | | 2 | 3 | 7 |
| 1[a] | H | H | 0 | 0 | 45 |
| 2[a] | Benzyl | H | 63 | 0 | 34 |
| 3[b] | Allyl | H | 96 | 0 | 0 |
| 4[c] | Benzyl | Ph | 0 | 35 | 0 |
| 5[c] | Cinnamyl | Ph | 0 | 72 | 0 |
| 6[a] | Crotyl | Me | 21 | 54 | 0 |

Yields were based on amides (1). General conditions: amide (0.30 mmol), THF / EtOH (8 ml / 2 ml), 0 ℃ a) $(PhSe)_2$ (0.60 mmol), $NaBH_4$ (0.60 mmol). b) $(PhSe)_2$ (0.15 mmol), $NaBH_4$ (0.30 mmol). c) $(PhSe)_2$ (0.30 mmol), $NaBH_4$ (0.30 mmol).

Oxidative deselenation of 2 gave the corresponding exomethylene lactams (8) in good yields (Scheme 2), which are expected to be useful building blocks for new types of fluorinated γ-lactams.




Scheme 2

**References and notes**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