Synthesis of 3-fluoroalkyl-2-aziridinyl ketones

O. G. Khomutov, V. I. Filyakova, and K. I. Pashkevich*

Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation. Fax: +7 (343) 244 4133

Simple and efficient methods for the synthesis of *trans*-3-fluoroalkyl-2-aziridinyl ketones from polyfluorinated α,β-enones have been developed.

Key words: *trans*-3-fluoroalkyl-2-aziridinyl ketones, β-aminoketones, α-bromo-α,β-enones, α,β-dibromoketones.

Aziridinyl ketones and their derivatives are widely known pharmacophores used in the development of anticancer and antileukemia drugs.[1] However, fluorinated aziridines are little studied because there have not been efficient methods for their preparation. Fluorinated aziridines have been synthesized by addition of diazomethane at a C=N bond followed by photolysis of the resulting fluorinated 1,2,3-triazolines,[2,3] as well as by nucleophilic elimination of fluoroolefins.[4] The first use of the Gabriel reaction for the synthesis of fluorinated aziridines was published only in 1986.[5] Later, the preparation of *N*-substituted 3-fluoromethyl-2-aziridinyl ketones by rearrangement of 3-fluoromethyl-4-isoxazolines that are difficult to obtain was reported.[6]

In the present work we developed versatile and efficient methods for the synthesis of 3-fluoroalkyl-2-aziridinyl ketones based on fluorine-containing α,β-enones. We found that the method for building the epoxide ring by iodination—dehydroiodination of fluorine-containing β-hydroxyketones proposed by us previously[7] can also be applied to the construction of the aziridine ring from β-aminoketones (**2**).*

N-Unsubstituted β-aminoketones **2** (Scheme 1) react with I_2 in the presence of K_2CO_3 to give *N*-unsubstituted aziridinyl ketones (**3**) in 67—83 % yields (Table 1). *N*-Alkyl substituted β-aminoketones are unstable and decompose into the starting compounds upon attempted isolation. However, when ethanol was used as the solvent, instead of *n*-hexane, *N*-alkyl substituted aziridinyl ketones **3** could be obtained directly from a mixture of α,β-enone (**1**), amine, and I_2, *i.e.*, without isolation of intermediate β-aminoketones **2**. *N*-Phenyl substituted β-aminoketones **2** do not react with I_2. Replacement of I_2 by Br_2 only results in bromination of the *N*-phenyl ring rather than in the formation of the three-membered ring (see Scheme 1).

* For the previous communication, see Ref. 8.

Scheme 1

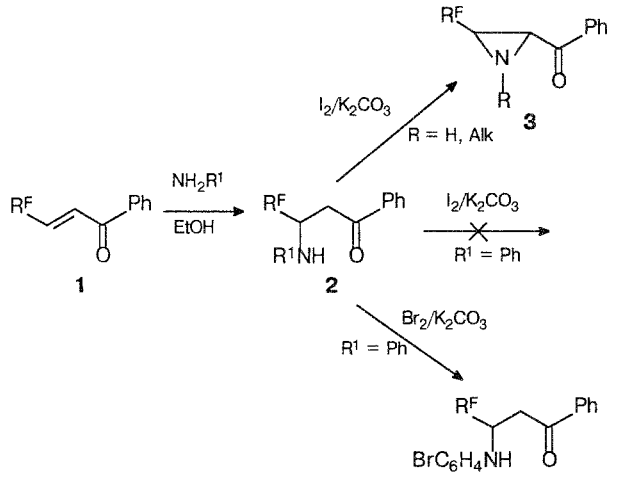


Table 1. Characteristics of 2-fluoroalkyl-2-aziridinyl ketones **3**

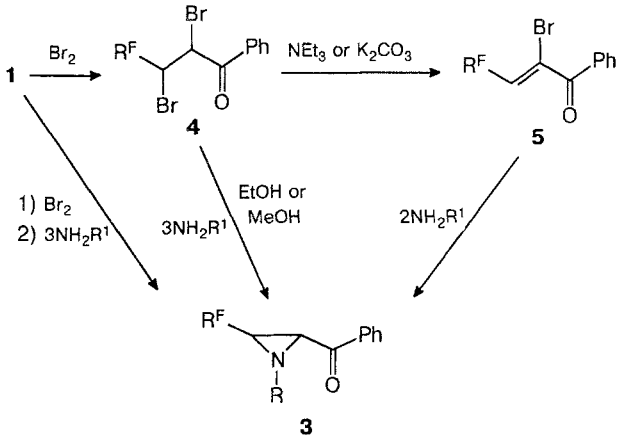
Compound	R^F	R^1	M.p. /°C	Yield (%) (method)
3a	CF_3	*n*-C_6H_{13}	Oil	68(D)
3b	CF_3	$(CH_2)_2OH$	Oil	72(D)
3c	CF_3	$CH_2C_6H_5$	55—56	83(D)
3d	CF_3	C_8H_5	119—120	87(E)
3e	C_6F_{13}	*n*-C_4H_9	Oil	74(D)
3f	C_8F_{17}	H	91—92	76(D)
3g	C_8F_{17}	CH_3	57—58	79(B)
3h	$H(CF_2)_4$	$(CH_2)_2OH$	Oil	67(C)
3i	$H(CF_2)_6$	H	53—54	83(A)
3j	$H(CF_2)_6$	*n*-C_6H_{13}	Oil	72(C)

A more versatile synthetic method, which makes it possible to vary the substituents at the N atom of the aziridine ring over a wide range, is the reaction of

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 282—284, February, 1994.

1066-5285/94/4302-0261 $12.50 © 1994 Plenum Publishing Corporation

Scheme 2



α-bromo-α,β-enones (**5**) with NH_3 and amines. Compound **5** can be generated *in situ* from **1** or α,β-dibromoketone **4**. The sequence of the reactions is given in Scheme 2. Bromination of compound **1** and dehydrobromination of **4** have been described in detail previously.[12] These reactions are carried out in an inert solvent (*n*-hexane). However, the stage in which the aziridine ring is formed (amination of **5**) requires a protic solvent (MeOH or EtOH). When an aprotic solvent is used at this stage, the process stops at compound **5**, and the ring closure does not occur.

Reactions of aromatic amines with both α-bromo-α,β-enones **5** and α,β-dibromoketones **4** result in the resinification of the reaction mixture. Nevertheless, *N*-phenyl substituted aziridinyl ketones **3** were successfully prepared with the aid of a modified procedure: by boiling a mixture of compound **5**, Et_3N, and an arylamine in MeOH.

The IR spectra of aziridinyl ketones **3** exhibit a band of the C=O stretching vibrations in the region 1700—1760 cm^{-1} (Table 2). The spectra of *N*-unsubstituted aziridinyl ketones **3** display as well a band at 3300 cm^{-1} (ν(NH)). The ^1H NMR spectra of **3** exhibit a multiplet for H(β) at 2.25—3.00 ppm and a signal for H(α) at 3.8—4.0 ppm, which is a doublet in the case of *N*-substituted aziridinylketones and a double doublet for *N*-unsubstituted aziridinyl ketones. The latter collapses into the doublet upon the addition of CD_3COOD. In contrast to nonfluorinated analogs, which are formed as mixtures of *cis*- and *trans*-isomers,[9] 3-fluoroalkyl-2-aziridinyl ketones **3** are produced exclusively in the *trans*-form, which is indicated by the magnitude of the

Table 2. Spectroscopic characteristics of aziridinyl ketones **3**

Compound	IR, ν/cm^{-1}		^1H NMR (δ, *J*/Hz)		
	C=O	NR^1	H(α)	H(β)	R^1
3a	1673	—	3.82 (d, J_1 = 2.3)	2.95—3.25 m	0.83—2.59 (m, 12 H, C_6H_{13})
3b	1655	3450	3.86 d	3.04—3.30 m	2.77 (t, $J_{CH_2CH_2}$ = 5.1, 2 H, CH_2OH) 3.66 (t, *J* = 5.1, 2 H, NCH_2)
3c	1670	—	3.79—3.87 (m, $+CH_2$)	3.28 d.q	3.83 (q, J_1 = 2.3, $J_{H(\beta)CF_3}$ = 4.92, H, CH_2)
3d	1675	—	4.35 (d, J_1 = 2.3)	3.67 d.q	6.74—7.24 (m, J_1 = 2.3, $J_{H(\beta)CF_3}$ = 4.9, 5 H, Ph)
3e	1675	—	3.89 (d, J_1 = 2.3)	3.05—3.22 m	2.67 (t, $J_{CH_2CH_2}$ = 6.8, 2 H, CH_2N) 0.90 (t, $J_{CH_3CH_2}$ = 6.7, 3 H, CH_3) 1.24 (m, 4 H, C_2H_8)
3f	1667	3207	3.87 (br.d, $J_{H(\alpha)NH}$ = 3.5)	2.62—2.87 m	2.17—2.55 (m, 1 H, NH)
3g	1670	—	3.88 (d, J_1 = 2.3)	2.5—2.83 m	2.68 (c, 3 H, CH_3)
3h	1680	3390	3.62—4.02 (m, $+CH_2OH$)	3.02—3.40 m	2.85 (t, $J_{CH_2CH_2}$ = 4.0, 2 H, CH_2N) 2.67—2.95 (1 H, OH)
3i	1680	3215	3.79 (d.d, J_1 = 2.5, $J_{H(\alpha)NH}$ = 8.75)	2.25—3.00 (m, 2 H, +NH)	2.25—3.00 (1 H, OH)
3j	1676	—	3.87 (d, J_1 = 2.58)	3.12 (t.d, J_1 = 2.58, $J_{H(\beta)CF_2}$ = 10.8)	0.82—2.64 (m, *n*-C_6H_{13})

Notes. Ph gives a multiplet at δ 7.30—8.22. The signals for $H(CF_2)_2$ and $H(CF_2)_4$ are exhibited at δ 5.99—6.12 as a triplet of triplets with $^2J_{H,F}$ = 51÷53 and $^3J_{H,F}$ = 4.9÷6.1 Hz.

spin coupling constant of the ring protons, which is equal to 2.3—2.5 Hz.[10]

Experimental

α,β-Enones **1** and β-aminoketones **2** were prepared by the known procedure;[11] α,β-dibromoketones **5** and α-bromo-α,β-enones **6** were synthesized as described in Ref. 12.

IR spectra were recorded on a Specord-75-IR spectrophotometer for liquid samples as 5 μ films and for solid samples as pastes with vaseline oil. ^{1}H NMR spectra were obtained on a Tesla-BS-567A spectrometer (100 MHz) with TMS as the internal standard. Chromatography was performed on a column packed with L 100/250 silica gel, $CHCl_3$ was used as the eluent.

Synthesis of 3-fluoroalkyl-2-aziridinyl ketones 3 (General procedure). A. From β-aminoketones 2. A mixture of equimolar amounts of a β-aminoketone **2**, K_2CO_3, I_2, and a solvent (saturated hydrocarbons, Freon-113) was stirred at 20 °C until decolorized, filtered, and cooled. The precipitated crystals were filtered off and reprecipitated from an ethereal solution with *n*-hexane.

B. From α,β-enones 1, amines, and I_2. An equimolar amount of I_2 and a threefold molar excess of an amine were added to a solution of **1** in benzene. The reaction mixture was kept until decolorized, washed with water and a solution of $Na_2S_2O_3$, dried with $MgSO_4$, and concentrated. The residue was chromatographed or recrystallized from *n*-hexane.

C. From α-bromo-α,β-enones 5. α-Bromo-α,β-enone **5** was dissolved in 96 % EtOH, and a twofold molar excess of NH_3 or a primary amine was added with stirring. (Liquids were added dropwise and gases were bubbled.) The mixture was kept for 2—3 h at 20 °C, EtOH was evaporated, and the residue was diluted with ether. The undissolved precipitate of amine hydrobromide was filtered off and the ether was evaporated. The residue was recrystallized from *n*-hexane or chromatographed.

D. From α,β-enones 1, Br_2, and amines. An equimolar amount of Br_2 was added dropwise to a stirred solution of **1** in *n*-hexane, the mixture was kept until decolorized and concentrated. The residue was dissolved in methanol, a threefold molar excess of amine was added, and the mixture was kept for 24 h at 20 °C. The solvent was evaporated, the residue was dissolved in ether, and the solution was washed with water. The ethereal layer was separated, dried with $MgSO_4$, and the ether was evaporated. The residue was recrystallized or chromatographed.

E. Synthesis of *N*-phenyl substituted 3 from α,β-dibromoketones 4. A mixture of **4**, a twofold molar excess of Et_3N, and an equimolar amount of aniline in MeOH was boiled for 3 h and kept for 24 h at 20 °C. The precipitate was filtered off, washed with water, and recrystallized from *n*-hexane.

References

1. P. A. Gembitskii, D. S. Zhuk, and V. A. Kargin, *Khimiya etilenimina* [*Chemistry of Ethyleneimine*], Moscow, Nauka, 1966, 218 p. (in Russian).
2. I. L. Knunyants and Yu. V. Zeifman, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 711 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16**, 695 (Engl. Transl.)].
3. R. G. Kostyanovskii, G. K. Kadorkina, G. V. Shustov, I. I. Chervin, Sh. S. Nasibov, and S. V. Varlamov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 145 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31**, 136 (Engl. Transl.)].
4. Yu. V. Zeifman, E. M. Rokhlin, U. Utebaev, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR*, 1976, **226**, 1337 [*Dokl. Chem.*, 1976, **226** (Engl. Transl.)].
5. Yu. L. Ignatova, N. M. Karimova, O. V. Kil'disheva, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 732 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 675 (Engl. Transl.)].
6. K. Tanaka, M. Ohsuga, Y. Sugimoto, Y. Okafuji, and K. Mitsuhashi, *J. Fluor. Chem.*, 1988, **39**, 39.
7. K. I. Pashkevich, V. I. Filyakova, and V. G. Ratner, *Zh. Org. Khim.*, 1987, **23**, 2625 [*J. Org. Chem.*, 1987, **23** (Engl. Transl.)].
8. V. I. Filyakova and K. I. Pashkevich, *Zh. Org. Khim.*, 1989, **25**, 2461 [*J. Org. Chem.*, 1989, **25** (Engl. Transl.)].
9. N. H. Cromwell and H. Hoeksema, *J. Am. Chem. Soc.*, 1949, **71**, 708.
10. P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, 1970, **35**, 888.
11. R. R. Latypov, V. D. Belogai, and K. I. Pashkevich, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 123 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 108 (Engl. Transl.)].
12. V. I. Filyakova, R. R. Latypov, and K. I. Pashkevich, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 2134 [*Russ. Chem. Bull.*, 1993, **42**, 2047 (Engl. Transl.)].

Received July 9, 1993