171. Synthesis of 1-Fluoro-2-amino-1,3-cyclohexadienes and 1-Fluorobicyclo[2.2.2]octan-2-ones

by **Heike Pick-Schliebs** and **Paul Margaretha***

Institut für Organische Chemie, Universität, D-2000 Hamburg 13

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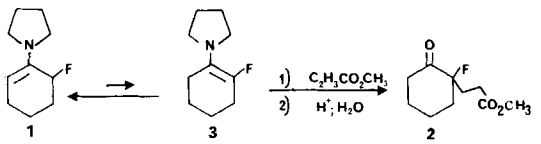
Conjugated β-fluoro-enamines **4** undergo cycloaddition to methyl acrylate regio- and stereospecifically, affording the 1-fluorobicyclo[2.2.2]octan-2-one **6a** after hydrolysis.

The synthesis of α-fluoro-imines from α-fluoro carbonyl compounds and primary amines has been reported [1] and their photochemistry investigated [2–4]. As for fluoroenamines, 2-fluorocyclohexanone reacts with pyrrolidine either in the presence of $MgSO_4$ at −10° [5] or molecular sieves at r.t. [6] to afford 6-fluoro-1-(1-pyrrolidinyl)cyclohexene (**1**) in very good yield. Fluoroenamine **1** reacts with methyl acrylate to give methyl 3-(1-fluoro-2-oxocyclohexyl)propionate (**2**) *via* the isomeric 1-fluoro-2-(1-pyrrolidinyl)cyclohexene (**3**) [6] *(Scheme 1)*.

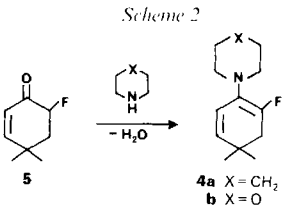
Scheme 1



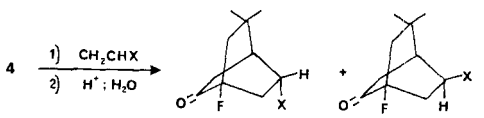
We now report on the synthesis and reactivity of 1-fluoro-2-piperidino- and 1-fluoro-2-morpholino-1,3-cyclohexadiene, **4a** and **4b**, respectively. To our knowledge, compounds of type **4** represent the first examples of β-fluorinated conjugated enamines. Compounds **4a** and **4b** were prepared from 6-fluoro-4,4-dimethyl-2-cyclohexenone (**5**) [7] and secondary amines with azeotropic removal of H_2O, a method already described for the synthesis of dienamines of 4,4-dimethyl- and 4,4,6-trimethyl-2-cyclohexenone [8] *(Scheme 2)*.

Dienamines **4** react with methyl acrylate in boiling dioxane regio- and stereospecifically (> 95%) to afford, after hydrolysis, the ester **6a**. The cycloaddition to acrylonitrile

Scheme 2



Scheme 3



6a X = CO_2Me > 19:1
b X = CN 3:1

7

is also regiospecific but only moderately stereoselective as determined by GC, affording **6b/7b** 3:1 *(Scheme 3)*. The ^{13}C-NMR spectra of **6b** and **7b** are alike. The spectral data of compounds **4** and **6** is summarized in the *Table*.

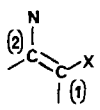
Some of the NMR parameters of dienamines **4** are worth mentioning. In the ^{1}H-NMR, $^4J(1,3)$ between *H*–C(3) and F (9.5 Hz) is much larger than the corresponding value (2.0 Hz) between *H*–C(3) and *H*–C(1) in the parent enamine [8]. In the ^{13}C-NMR, a pronounced effect of fluorine on the chemical shifts of C(1) and C(2) is observed.

The reactivity of the dienamines toward acrylic-acid derivatives is also strongly influenced by F-substitution. Thus, **4a** or **4b** react more then twice as fast as the parent (H) dienamine in boiling dioxane (monitoring by GC). While the parent dienamine and

Table. *Spectroscopic Data of Compounds* **4** *and* **6**

	^{1}H-NMR[a])[b])	^{13}C-NMR[a])[b])[c])	MS (70 eV)
4a	5.60 (*t*, *J* = 9.5, H–C(3)); 5.28 (*d*, *J* = 9.5, H–C(4)); 2.25 (*d*, *J* = 6.0, 2 H–C(6))	146 (*d*, *J* = 264.0, C(1)); 134 (*dd*, *J* = 4.0, C(3)); 123 (*d*, *J* = 5.0, C(2))	
4b	1.00 (*s*, 6H, CH_3)	122 (*dd*, *J* = 2.5, C(4)); 40 (*dt*, *J* = 20.0 C(6)); 28 (*q*, CH_3)	211 ($M^{+\cdot}$, 87) *196*
6a	3.75 (*s*, CH_3O); 3.35 (*ddd*, *J* = 12.5, 6.0, 2.5, C*H*COOMe); 2.60 (*dq*, *J* = 18.8, 2.5, CHCO); 2.50 (*dddd*, *J* = 11.0, 6.0, 5.0, 1.0, *H*CH–CH *trans*); 2.38 (*ddd*, *J* = 18.8, 2.0, 1.0, CHCO); 2.10 (*ddd*, *J* = 12.5, 11.0, 6.0, *H*CH–CH *cis*); 2.05 (*dt*, *J* = 2.0, 2.5, H–C(1)); 1.80 (*m*, $CH_2C(CH_3)_2$); 1.28, 1.10 (*s*, CH_3)	207 (*d*, *J* = 15.0, CO); 174 (*s*, $COOCH_3$); 95 (*d*, *J* = 204.0, CF); 52 (*q*, CH_3O); 44 (*dt*, *J* = 16.3, CH_2); 41 (*d*, C(1)); 39 (*dd*, *J* = 10.0, $CHCOOCH_3$); 38 (*t*, CH_2CO); 34 (*d*, *J* = 9.0, $(CH_3)_2C$); 30 & 29 (*q*, CH_3); 29 (*dt*, *J* = 24.0, CH_2)	228 ($M^{+\cdot}$, 9) *127*
6b	3.55 (*ddd*, *J* = 12.0, 6.0, 2.5, CHCN); 2.80 (*m*, CH_2CO); 2.40 (*dt*, *J* = 6.0, 12.0, *H*CH–CH *cis*); 1.90 (*m*, HC*H*–CH *trans*); 2.02 (*dt*, *J* = 2.0, 2.5, H–C(1)); 1.85 (*m*, $CH_2C(CH_3)_2$); 1.28, 1.15 (s, CH_3)	205 (*d*, *J* = 14.0, CO); 121 (*s*, CN); 93 (*d*, *J* = 205.0, CF); 43 (*dt*, *J* = 16.0, CH_2); 41 (*d*, C(1)); 38 (*t*, CH_2CO); 34 (*d*, *J* = 9.0 $(CH_3)_2C$); 30 (*dt*, *J* = 23.0, CH_2); 30 & 29 (*q*, CH_3); 25 (*dd*, *J* = 11.0, *C*HCN)	[d])195 ($M^{+\cdot}$, 46) *126*

[a]) In $CDCl_3$.
[b]) Signals of amino component not indicated.
[c]) Values of *J*(C,F) given.
[d]) **6b/7b** (3:1 mixture).



	X	δ (CDCl$_3$) H [8]	CH_3 [8]	F
C(1)		99	123	146
C(2)		145	138	122

other cross conjugated dienamines react with these electrophilic olefins to afford mixtures of cycloadducts and alkylation products [9], dienamines **4** undergo cycloaddition to methyl acrylate regio- and stereospecifically, and to acrylonitrile again regiospecifically and stereoselectively. The constitution of ketones **6** is established both by ^{13}C-NMR, wherein the J(C,F) values for both CH_2 groups, non-vicinal to the CO group are similar (23 and 16 Hz) and larger than for the *C*HX (X = COOMe or CN; 11 Hz), and by ^{1}H-NMR, wherein a vicinal coupling between CHX and the bridgehead CH (J = 2.5 Hz) is observed [10]. The stereoselectivity most probably arises from interaction between the geminal methyl groups and the substituent (X) on the alkene, and, therefore, X is located (exclusively for X = $COOCH_3$ and mainly for X = CN) *'syn'* to the NH_2 and then *'endo'* to the CO group. This assignment is in agreement with the observed ^4J value of 2.5 Hz between CHX and one of the CHCO H-atoms suggesting a *W*-geometry [10].

Further work on the photochemistry of ketones **6** and on their conversion to the parent 1-fluoro-3,3-dimethylbicyclo[2.2.2]octane is now in progress.

A generous gift of FSO_3H by *Bayer AG*, Leverkusen, is gratefully acknowledged.

Experimental Part

General. See [8]. Enone **5** was synthesized according to [7]. Anal. GC was performed on a *SE 30* capillary column.

1-Fluoro-5,5-dimethyl-2-piperidino- and 1-Fluoro-5,5-dimethyl-2-morpholino-1,3-cyclohexadienes (**4a** and **4b**, resp.). A sol. of *6-fluoro-4,4-dimethyl-2-cyclohexanone* (**5**; $4 \cdot 10^{-2}$ mol) and corresponding amine ($8 \cdot 10^{-2}$ mol) in 30 ml of benzene is refluxed under N_2 for 12–15 h, until all the H_2O has separated on a *Dean-Stark* trap. After evaporation of the solvent, bulb-to-bulb distillation (120°/0.01 Torr) affords **4a** (60%) or **4b** (61%), respectively. Both dienamines **4** decompose on standing at r.t., but can be stored at −10° for about two weeks.

Methyl 4-Fluoro-5-oxo-7,7-dimethylbicyclo[2.2.2]octane-2-carboxylate and 4-Fluoro-5-oxo-7,7-dimethylbicyclo[2.2.2]octane-2-carbonitrile (**6a** and **6b**, resp.). A soln. of **4a** (10^{-2} mol) and methyl acrylate or acrylonitrile ($1.1 \cdot 10^{-2}$ mol) in 10 ml of dioxane is refluxed under N_2 for 6–8 h. The solvent is then evaporated and the residue stirred with 1N HCl for 30 min at r.t. After extraction with pentane, washing of the pentane extract with sat. $NaHCO_3$- and NaCl solns., drying ($MgSO_4$), evaporation of the solvent, and bulb-to-bulb distillation (100°/0.01 Torr) affords **6a** (40%) or **6b**/**7b** (37%) 3:1, respectively. Similar results and yields are obtained from dienamine **4b**.

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