[4+2]-Cycloaddition reactions employing 2-fluoro-2-alkenal *N,N*-dimethylhydrazones: synthesis of 3-fluoropyridines and dihydro or tetrahydro derivatives thereof

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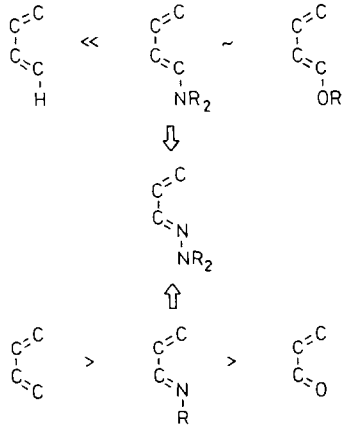
(Received January 15, 1993; accepted April 6, 1993)

Abstract

N,N-Dimethylhydrazones prepared from 2-fluoro-2-alkenals undergo smooth [4+2]-cycloaddition reactions with methyl acrylate, dimethyl acetylenedicarboxylates and quinones. The resulting 3-fluoropyridines, or dihydro and tetrahydro derivatives thereof, can be isolated in fair to good yield.

Introduction

The attachment of a donor substituent such as dialkylamino, alkyloxy or silyloxy to the periphery of a diene enhances its reactivity towards dienophiles immensely [1]. On the other hand, when electronegative heteroatoms such as oxygen or nitrogen are inserted into the backbone of the diene, replacing a methylene or methine moiety, a rate retardation is the consequence, at least as long as the 'normal' electron demand is operative. If the two modes of substitution occur simultaneously, the opposing effects tend to cancel each other. In general, however, the remaining reactivity is still sufficient to bring about smooth [4+2]-cycloadditions. A very typical case of this kind was described by Ghosez *et al.* [2] who successfully employed α,β-unsaturated *N,N*-dimethylhydrazones in Diels–Alder-type reactions.



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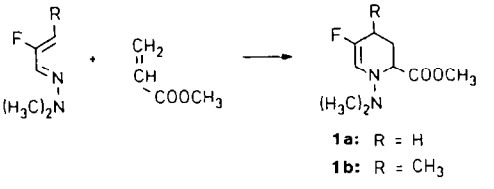
Results

Fluorine substitution is known to diminish the cycloaddition performance of dienes, although only slightly [3]. 2-Fluoro-2-alkenals [4] being readily available, we have converted them into *N,N*-dimethylhydrazones and have studied the behaviour of the latter compounds towards dienophiles.

As expected, the cycloaddition reaction between the *N,N*-dimethylhydrazone of 2-fluoroacrolein and methyl acrylate took place under fairly mild conditions (100 °C). The cycloadduct **1a** bearing the ester function at the nitrogen-bonded carbon atom was isolated as the sole regioisomer. A similar reaction was accomplished between the *N,N*-dimethylhydrazone of 2-fluoro-2-butenal and methyl acrylate giving the tetrahydropyridine derivative **1b**.

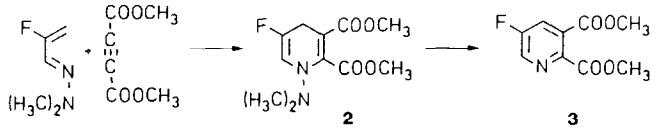


1a: R = H

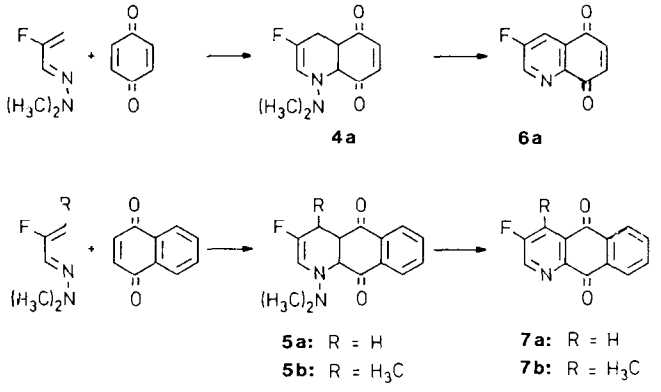
1b: R = CH_3

Dimethyl acetylenedicarboxylate reacted rapidly at 80 °C to afford a stable 1,4-dihydropyridine derivative **2**. Upon acid-catalyzed elimination of dimethylamine, the aromatized dimethyl 5-fluoro-2,3-pyridinedicarboxylate (**3**) was obtained.

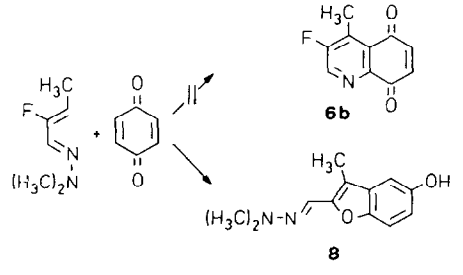
SSDI 0022-1139(93)02932-5



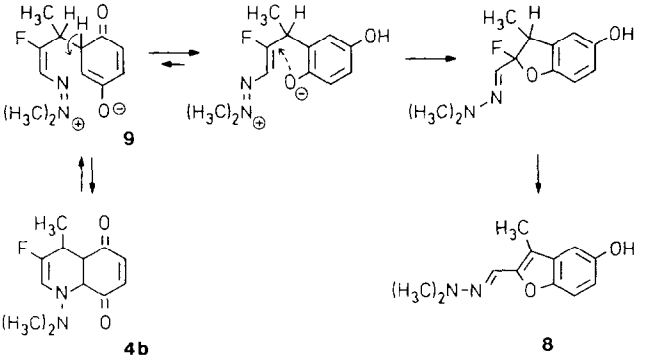
p-Benzoquinone and 1,4-naphthoquinone formed the cycloadducts **4a**, **5a** and **5b** at ambient temperature. Without isolation, these intermediates were consecutively treated with silica gel and manganese dioxide. Concomitant oxidation and elimination of dimethylamine produced the quininedione **6a** and the benzoquininediones **7a** and **7b**.



The reaction took a different course, when *p*-benzoquinone was allowed to react with the *N,N*-dimethylhydrazone of 2-fluoro-2-butenal. Rather than the expected cycloadduct **6b**, a halogen-free product was obtained to which the benzofuran structure **8** was tentatively assigned.



Although several details still remain obscure, the formation of **8** can be rationalized by assuming the intermediacy of a ring-opened zwitterion **9** [5]. Rather than collapse to give the cycloadduct **4b**, zwitterion **9** could then have undergone tautomerization, cyclization and hydrogen fluoride elimination.



Experimental

General

Starting materials were purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim) or Merck-Schuchardt (Darmstadt), unless literature sources or details of the preparation are given. All commercial reagents were used without further purification.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids, a spatula tip of hydroquinone or potassium carbonate was added.

Room temperature (22–26 °C) is consistently indicated as 25 °C. Melting ranges (m.p.) were reproducible after resolidification, unless otherwise stated (dec.), and were corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product failed even at temperatures as low as −75 °C. If reduced pressure is not specified, boiling ranges were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

Silica gel (Merck Kieselgel 60) of 70–230 mesh (0.06–0.20 mm) particle size was used for column chromatography. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of this liquid was still some 3–5 cm above the silica layer, the dry powder, obtained by absorption of the crude product mixture on 15–20 g silica gel and subsequent evaporation of the solvent, was poured on top of the column.

Nuclear magnetic resonance spectra (Bruker-Spectrospin AC-250 instrument) of hydrogen-1 nuclei were recorded at 250 MHz and of carbon-13 nuclei at 90.6 MHz; deuterochloroform was used as the solvent, unless otherwise stated. Chemical shifts δ refer to the signal of tetramethylsilane. Coupling constants (J) were measured in Hz. Abbreviations of coupling patterns: s (singlet), d (doublet), t (triplet), q (quadruplet), td (triplet of doublets) and m (multiplet).

Mass spectra were obtained at 70 eV ionization potential maintaining a source temperature of 200 °C. Elementary analyses were made by the laboratory of I. Beetz, D(W)-8640 Kronach, Germany.

Starting material

2-Fluoropropenal dimethylhydrazone

2-Fluoropropenal [6] (11 g, 0.15 mol) was added dropwise under stirring to an ice-cold solution of *N,N*-

dimethylhydrazone (9.0 g, 0.15 mol) and sodium dihydrogen phosphate (18 g, 0.15 mol) in water (50 ml). After an additional 45 min at 0 °C, the mixture was extracted with diethyl ether (2×0.10 l), washed with brine (2×50 ml), dried and distilled. The product was collected over the boiling range 44–45 °C/6 mmHg, n_D^{20} 1.5118, 11 g (63%). ^{1}H NMR δ: 6.61 (1 H, d, J=17.0 Hz); 4.76 (1 H, dd, J=16.4, 3.1 Hz); 4.52 (1 H, dd, J=48.1, 3.1 Hz); 2.98 (6 H, s). Analysis: Calc. for $C_5H_9FN_2$ (116.14): C, 51.71; H, 7.81%. Found: C, 51.66; H, 7.76%.

(E)-2-Fluoro-2-butenal dimethylhydrazone

This was prepared in a similar manner from (*E*)-2-fluoro-2-butenal [4] (18 g, 0.20 mol), but with heating of the reaction mixture over 30 min to 55 °C. Yield 76%, m.p. 10–11 °C, b.p. 49–50 °C/2.5 mmHg, n_D^{20} 1.5130. ^{1}H NMR δ: 6.62 (1 H, d, J=17.5 Hz); 4.90 (1 H, dq, J=37.9, 7.2 Hz); 2.89 (6 H, s); 1.74 (3 H, dd, J=7.2, 2.3 Hz). MS *m/z*: 130 (100%, M^+); 86 (35%). Analysis: Calc. for $C_6H_{11}FN_2$ (130.16): C, 55.37; H, 8.52%. Found: C, 55.43; H, 8.54%.

Cycloadducts formed with methyl acrylate

*Methyl 1-dimethylamino-5-fluoro-1,2,3,4-tetrahydro-2-pyridinecarboxylate (**1a**)*

2-Fluoropropenal dimethylhydrazone (0.58 g, 5.0 mmol) and methyl acrylate (1.7 g, 20 mmol) were dissolved in toluene (10 ml) and heated for 50 h at 100 °C. The product was purified by chromatography on silica gel as the support, using a 1:1 (v/v) mixture of ethyl acetate and hexane as the eluent. After distillation, 0.53 g (52%) of **1a** was collected, b.p. 65–70 °C/1 mmHg, n_D^{20} 1.4735. ^{1}H NMR δ: 6.12 (1 H, dd, J=10.8, 1.8 Hz); 3.76 (3 H, s); 3.58 (1 H, ddd, J=9.8, 4.9, 1.3 Hz); 2.5 (1 H, m); 2.41 (6 H, s); 2.3 (1 H, m); 2.1 (2H, m). MS *m/z*: 202 (37%, M^+); 116 (100%). Analysis: Calc. for $C_9H_{15}FN_2O_2$ (202.23): C, 53.45; H, 7.48%. Found: C, 53.45; H, 7.26%.

*Methyl 1-dimethylamino-5-fluoro-1,2,3,4-tetrahydro-4-methyl-2-pyridinecarboxylate (**1b**)*

A similar reaction was carried out with (*E*)-2-fluoro-2-butenal dimethylhydrazone (0.66 g, 5.0 mmol), but heating at 100 °C was extended to 100 h to give 0.449 (41%) of **1b**, b.p. 70–74 °C/1 mmHg, n_D^{20} 1.4698. ^{1}H NMR δ: 6.07 (1 H, dd, J=11.0, 2.3 Hz); 3.77 (3 H, s); 3.58 (1 H, dd, J=12.0, 2.5 Hz); 2.72 (1 H, symm. m); 2.40 (6 H, s); 2.14 (1 H, symm. m); 1.78 (1 H, ddd, J=13.0, 12.0, 10.8 Hz); 1.09 (3 H, dd, J=6.7, 0.8 Hz). MS *m/z*: 216 (100%, M^+); 130 (28%). Analysis: Calc. for $C_{10}H_{17}FN_2O_2$ (216.25): C, 55.54, H, 7.92%. Found: C, 55.52, H, 7.99%.

Cycloadducts formed with dimethyl acetylenedicarboxylate

*Dimethyl 1-dimethylamino-5-fluoro-1,4-dihydro-2,3-pyridinedicarboxylate (**2**)*

A solution consisting of 2-fluoropropenal dimethylhydrazone (0.58 g, 5.0 mmol), dimethyl acetylenedicarboxylate (1.4 g, 10 mmol) in toluene (10 ml) was heated for 50 h at 80 °C. The product was purified by chromatography on silica gel using a 2:1 (v/v) mixture of hexane and ethyl acetate as the eluent, giving 0.81 g (63%) of **2**, m.p. 119–120 °C (from acetone/hexane). ^{1}H NMR δ: 6.11 (1 H, dt, J=8.5, 1.3 Hz); 3.88 (3 H, s); 3.70 (3 H, s); 3.39 (2 H, d, J=1.2 Hz); 2.52 (6 H, s). MS *m/z*: 258 (46% M^+); 182 (100%). Analysis: Calc. for $C_{11}H_{15}FN_2O_4$ (258.25); C, 51.16; H, 5.85%. Found: C, 51.29; H, 6.00%.

*Dimethyl 5-fluoro-2,3-pyridinedicarboxylate (**3**)*

A small amount of the dihydropyridine derivative **2** (0.52 g, 2.0 mmol) was dissolved in toluene (5 ml) and stirred for 45 min with a small amount of concentrated hydrochloric acid (0.5 ml). The mixture was absorbed on a little silica gel, dried and poured on top of a column filled with fresh silica gel under hexane. Elution with a 1:1 (v/v) mixture of ethyl acetate and hexane afforded 0.32 g (75%) of **3**, m.p. 69–70 °C (from acetone/hexane). ^{1}H NMR δ: 8.64 (1 H, d, J=2.8 Hz); 7.85 (1 H, dd, J=8.1, 2.8 Hz); 4.01 (3 H, s); 3.97 (3 H, s). MS *m/z*: 213 (9%, M^+); 182 (61%); 96 (100%). Analysis: Calc. for $C_9H_8FNO_4$ (213.16): C, 50.71; H, 3.78%. Found: C, 50.62; H, 3.98%.

Cycloadducts formed with quinones

*3-Fluoro-5,8-quinolinedione (**6a**)*

2-Fluoropropenal dimethylhydrazone (0.58 g, 5.0 mmol) in toluene (5 ml) was added dropwise to an ice-cold suspension of *p*-benzoquinone (1.1 g, 10 mmol) in toluene. Stirring was continued for 50 h at 25 °C. The solvent was evaporated and replaced by ethyl acetate (0.10 l). After addition of silica gel (30 g), the dark mixture was stirred for 1 h at 25 °C before being filtered and concentrated. The residue was dissolved in diethyl ether (0.25 l) and manganese dioxide (30 g) was added. After stirring for 1 h at 25 °C, the organic material was absorbed on silica gel. Elution from a silica gel column with a 1:1 (v/v) mixture of ethyl acetate and hexane afforded 0.55 g (62%) of **6a**, m.p. 123–124 °C (from diethyl ether/hexane). ^{1}H NMR δ: 8.90 (1 H, d, J=2.8 Hz); 8.10 (1 H, dd, J=7.4, 2.8 Hz); 7.19 (1 H, d, J=10.4 Hz); 7.11 (1 H, dd, J=10.4, 0.7 Hz). MS *m/z*: 177 (61%, M^+); 149 (35%); 121 (100%). Analysis: Calc. for $C_9H_4FNO_2$ (177.13): C, 61.03; H, 2.28%. Found: C, 61.01, H, 2.37%.

3-Fluorobenzo[g]quinoline-5,10-dione (7a)

Applying the same procedure as described above, but using 1,4-naphthoquinone (1.6 g, 10 mmol) instead of *p*-benzoquinone, 0.65 g (57%) of **7a** was obtained, m.p. 214–215 °C (from acetone/hexane). ^{1}H NMR (D_3CCOCD_3) δ: 9.05 (1 H, d, J=3.0 Hz); 8.3 (3 H, m); 8.03 (2 H, symm. m). MS *m/z*: 227 (100%, M^+); 199 (42%); 171 (53%). Analysis: Calc. for $C_{13}H_6FNO_2$ (227.19): C, 68.73; H, 2.66%. Found: C, 69.04; H, 2.78%.

3-Fluoro-4-methylbenzo[g]quinoline-5,10-dione (7b)

In the same way, (*E*)-2-fluoro-2-butenal dimethylhydrazone (0.65 g, 5.0 mmol) and 1,4-naphthoquinone gave 0.60 g (50%) of **7b**, m.p. 206–207 °C (from acetone/hexane). ^{1}H NMR δ: 8.85 (1 H, d, J=0.5 Hz); 8.40 (1 H, symm. m); 8.29 (1 H, symm. m); 7.85 (2 H, symm. m); 2.85 (3 H, d, J=2.1 Hz). MS *m/z*: 241 (100%, M^+); 213 (52%). Analysis: Calc. for $C_{14}H_8FNO_2$ (241.22): C, 69.71; H, 3.34%. Found: C, 70.11; H, 3.05%.

5-Hydroxy-3-methylbenzofuran-2-carbaldehyde dimethylhydrazone (8)

The reaction between (*E*)-2-fluoro-2-butenal dimethylhydrazone (10 mmol) and *p*-benzoquinone (10 mmol) afforded a main product to which structure **8** was assigned on the basis of its spectral data, 0.85 g (38%), m.p. 159–160 °C (from diethyl ether/hexane). ^{1}H NMR (D_3CCOCD_3) δ: 8.22 (1 H, s; signal disappears upon treatment with D_2O); 7.28 (1 H, s); 7.21 (1 H, d, J=8.3 Hz); 6.89 (1 H, d, J=2.5 Hz); 6.77 (1 H, dd, J=8.6, 2.5 Hz); 2.98 (6 H, s); 2.28 (3 H, s). ^{13}C NMR δ: 151.3 (s); 149.8 (s); 149.0 (s); 131.3 (s); 121.3 (d, J=161 Hz); 112.8 (d, J=159 Hz); 112.4 (s); 111.5 (d, J=164 Hz); 104.1 (d, J=160 Hz); 42.7 (q, J=136 Hz); 8.0 (q, J=128 Hz). MS *m/z*: 218 (100%, M^+); 203 (9.4%); 131 (16%). Analysis: Calc. for $C_{12}H_{14}N_2O_2$ (218.25): C, 66.04; H, 6.47%. Found: C, 66.17; H, 6.40%.

Acknowledgment

This work was financially supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, Berne, and the Ciba-Geigy AG, Basle. The authors are also indebted to Dr Guo-qiang Shi, Shanghai for many valuable suggestions.

References

1 F. Fringuelli and A. Taticchi, *Dienes in the Diels–Alder Reaction*, Wiley, New York, 1990, pp. 63–96; see also S. Danishefsky, *Acc. Chem. Res., 14* (1981) 400.
2 B.S. Poncin, A.M.H. Frisque and L. Ghosez, *Tetrahedron Lett., 23* (1982) 3261.
3 G.-q. Shi and M. Schlosser, *Tetrahedron, 49* (1993), in press.
4 Y. Bessière, Dang Ngoc-Huê Savary and M. Schlosser, *Helv. Chim. Acta, 60* (1977) 1739.
5 R. Sustmann, M. Rogge, U. Nüchter and H. Bandmann, *Chem. Ber., 125* (1992) 1657.
6 J. Buddrus, F. Nerdel, P. Hentschel and D. Klamann, *Tetrahedron Lett.*, (1966) 5379; H. Molines, T. Nguyen and C. Wakselman, *Synthesis*, (1985) 754.