Monatshefte für Chemie 131, 889–893 (2000)

Monatshefte für Chemie
Chemical Monthly

On the Reaction between 1-Aza-1,3-dienes and Push-Pull Olefins of the Acyloxymethylidene-malononitrile Type

Czeslawa Orlewska[1], **Rafat M. Shaker**[2], **Martin Dees**[3,a], and
Hans-Hartwig Otto[3,*]

[1] Department of Organic Chemistry, Faculty of Pharmacy, Medical University of Gdansk, PL-80416 Gdansk, Poland
[2] Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt
[3] Institute of Pharmacy, Pharmaceutical/Medicinal Chemistry, University of Greifswald, D-17487 Greifswald, Germany

Summary. The reaction between push-pull olefins of the acyloxymethylidene-malononitrile type and α,β-unsaturated hydrazones affords selectively 5-alkyl-2-cyano-6-(N′,N′-dimethylhydrazono)-hexa-2,4-dienenitriles. No [4+2]-cycloaddition products were detected. The structure elucidation of the obtained compounds and possible reaction mechanisms are discussed.

Keywords. Push-pull olefins; Hydrazones, α,β-unsaturated.

Introduction

In a preceeding paper we have reported about the *Diels-Alder* reaction between push-pull olefins and cyclic dienes [1]. Cycloaddition is among the most important routes for the synthesis of nitrogen-containing six-membered rings [2]. Of the various types of dienes used in this reaction, dimethylhydrazones of acrolein (**1**) have been rarely employed as 1-azadienes. A limited number of 1,3-azadienes, especially those with small alkyl substituents in the α-position, have been described as isolable and stable compounds [3]. Reactions of **1a** and **1b** with electron-poor dienophiles have been used in some examples for the synthesis of pyridines and dihydropyridines [4]. In continuation of our previous studies, we were interested in exploring the question if these azadienes are suitable substrates for *Diels-Alder* reactions with acyloxymethylidene-malononitriles (**2**). These compounds serv as push-pull dienophiles due to the substitution with two electron-withdrawing groups at the β-position relative to the O-acyl group and have not yet been used in hetero-*Diels-Alder* reactions.

---

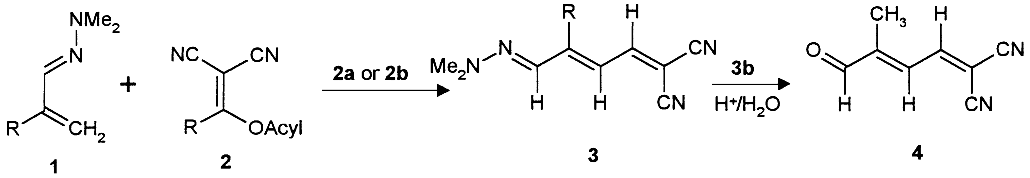
[a] Part of the PhD Thesis of *M. Dees*, University of Freiburg, 1995

[*] Corresponding author

Results and Discussion

Compounds **2a** and **2b** were prepared from malononitrile according to literature procedures [5]. To obtain **2c**, malononitrile was acetylated [6], followed by benzoylation with benzoyl chloride in the presence of triethylamine. **2a** and **2c** are stable, crystalline compounds which can be stored at room temperature, whereas **2b** is a colorless viscous liquid decomposing within a few days.

When **1a** was reacted with equimolar amounts of **2a** in benzene at room temperature for 72 h, deep red crystals of **3a** were obtained with a yield of *ca.* 55%; no other products were found. The reactions between **1b** and equimolar amounts of **2a** or **2b** under the same conditions for 24 h gave compound **3b** (*ca.* 80%) in both cases. Similarly, 2-ethyl-2-propenal dimethylhydrazone (**1c**) and the 2-butyl derivative **1d** reacted with **2a** afforded the analogous ethyl derivative **3c** (45%) and the butyl derivative **3d** (42%).



a: *R* = H
b: *R* = CH_3
c: *R* = C_2H_5
d: *R* = $(CH_2)_3CH_3$

a: *R* = H, Acyl = $CO\text{-}C_6H_5$
b: *R* = H, Acyl = $CO\text{-}CH_3$
c: *R* = CH_3, Acyl = $CO\text{-}C_5H_5$

a: *R* = H
b: *R* = CH_3
c: *R* = C_2H_5
d: *R* = $(CH_2)_3CH_3$

Scheme 1

All products are deeply red, stable ctystalline compounds. From elementary analyses and MS it was established that all reactions occurred with loss of one equivalent of the parent acid (acetic, benzoic). The IR spectra show a strong absorption band of the nitrile groups at 2210–2220 cm^{-1}. All ^1H NMR spectra are similar and show a singlet for the protons of the dimethylamino group around $\delta = 6.75$–6.90 ppm, and an AB system arising from two vicinal protons at $\delta = 6.35$–6.51 and 7.75–7.82 ppm with coupling constants between 10 and 13 Hz. These data are strong arguments for the open chain 1-azahexatriene structure **3**. In addition, ^1H NMR spectra of **3a** and **3b** reveal that these compounds consist of mixtures of the all-(*E*) isomer with small amounts of the (*Z*) isomer. Calculations of chemical shifts according to the method of *Simon et al.* [7] result in the following values for structure **3b** (calcd./found; δ in ppm): 3-H: 7.82/7.82, 4-H: 6.51/6.51, 6-H: 5.55–6.5/6.90. Similar correspondencies were found for the other compounds.

To prove the hydrazono structure of the products, a heterocorrelated ^1H-^{15}N NMR spectrum of **3d** was recorded. It shows two signals at -6 and -252 ppm, both coupled with the $(CH_3)_2N$ protons and the proton at C-6 of the azatriene system of **3**, corresponding to the sp^2 and sp^3 nitrogen atoms in the hydrazono group in **3d**. The ^{15}N NMR spectra of **3a** and **3b** show $\delta_{-N=} = 0$ or -5 ppm, respectively, and $\delta_{Me_2N} = -252$ ppm, thus supporting the proposed structure. Furthermore, the UV spectrum of **3b** in methanolic solution shows an intensive band at $\lambda = 447$ nm ($\varepsilon = 43500$) which can be interpreted as a $\pi \rightarrow \pi^*$ band of the conjugated system in **3**.

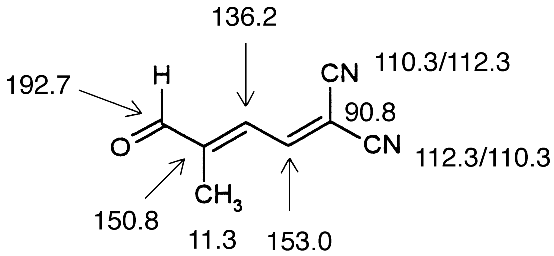


Fig. 1. ^{13}C NMR data of **4**

Finally, compound **3b** was hydrolyzed in diluted hydrochloric acid to the parent aldehyde **4**, whose UV spectrum shows an absorption maximum at $\lambda = 297\,\text{nm}$ ($\varepsilon = 24800$). The IR spectrum of **4** exhibits the characteristic absorption bands of the nitrile group ($2233\,\text{cm}^{-1}$), the carbonyl group ($1692\,\text{cm}^{-1}$), and the aldehyde C–H moiety ($2857\,\text{cm}^{-1}$). The presence of the aldehyde group was also confirmed by the ^{1}H NMR spectrum, of **4**, showing a singlet at $\delta = 9.71$ ppm. In addition, NOE spectra and solvent effects ($CDCl_3$ *vs.* benzene-d_6) prove unequivocally the all-(*E*) configuration. ^{1}H and ^{13}C NMR peak assignments were obtained from ^{1}H-^{13}C correlation experiments. The ^{13}C NMR data are summarized in Fig. 1.

It has to be noted that all reactions between **1** and **2c** completely failed (reaction times up to 5 d), suggesting that a second substituent at C-β of the acrylonitrile probably inhibits the addition reaction. On the other hand, smaller substituents with hyperconjugative effects in position 3 of the heterodiene (**1b**) facilitate the reaction. Bulkier substituents result in a diminished reactivity, probably due to steric effects (**1c,d**).

Experimental

General

M.p.: Linström apparatus (uncorr.); IR spectra: Perkin-Elmer IR 841, KBr if not noted otherwise; ^{1}H NMR spectra: Varian T 60, Bruker WP 80, WP 250, WM 400, internal *TMS*, δ in ppm, $CDCl_3$ if not noted otherwise; ^{13}C NMR spectra: Varian U 300 (75.43 MHz), internal *TMS*, δ in ppm; ^{1}H-^{15}N NMR spectra (HMBC): Varian Gemini 500, external nitromethane; MS: Finningan MAT 8430. Elemental analyses were performed at the *Pharmazeutisches Institut der Universität Freiburg*; the results agreed with the calculated values within experimental error. *THF* was dried over KOH refluxed with benzophenone and sodium, and then distilled. Other solvents were dried/purified according to literature procedures. The hydrazones of α,β-unsaturated aldehydes (**1**) were prepared according to methods given in the literature [8]; 2,2-dicyanovinyl benzoate (**2a**) and 2,2-Dicyanovinyl acetate (**2b**): see Ref. [1].

2,2-Dicyanovinyl-1-methylvinyl benzoate (**2c**; $C_{12}H_8N_2O_2$)

By an analogous method as described for **2a**, compound **2c** is obtained from acetylmalononitrile (3.24 g, 0.03 mol), benzoyl chloride (4.25 g, 0.03 mol), and triethylamine (0.03 mol).

Yield: 3.6 g (57%); colorless crystals; m.p.: 154°C (*n*-hexane); IR: $\nu = 3100, 3075, 3055, 3020, 2928$ (CH), 2245 (CN), 1756 (CO), 1616 (C=C) cm^{-1}; ^1H NMR (60 MHz): $\delta = 2.67$ (s, 3H, CH_3), 7.40–8.30 (m, 5H. arom. H) ppm.

Synthesis of **3** *(general procedure)*

An equimolar amount of freshly prepared hydrazone **1** is added to a stirred solution of **2** in 20 cm^3 benzene. Stirring is continued for the time noted below at room temperature under an atmosphere of N_2 or argon. Then the mixture is concentrated *in vacuo*, and a few drops of diethyl ether are added to the residue. The precipitate is collected and purified by CC (silica gel).

2-Cyano-6-(N′,N′-dimethylhydrazono)-hexa-2,4-dienenitrile (**3a**; $C_9H_{10}N_4$)

A mixture of **1a** (1.0 g, 10 mmol) and **2a** (2.0 g, 10 mmol) is stirred for 72 h. The residue is purified by CC (toluene:diethyl ether = 9:1).

Yield: 950 mg (55%); red crystals; m.p.: 136–138°C (benzene/petroleum ether); IR: $\nu = 2218$ (CN) cm^{-1}; ^1H NMR (80 MHz); $\delta = 3.13$ (s, 6H, $N(CH_3)_2$), 6.27–7.25 (m, 4H, 3-H, 4-H, 5-H, 6-H) ppm; MS: $m/z = 174$ (100%, M^+).

2-Cyano-5-methyl-6-(N′,N′-dimethylhydrazono)-hexa-2,4-dienenitrile (**3b**; $C_{10}H_{12}N_4$)

A mixture of **1b** (1.1 g, 10 mmol) and **2a** (2.0 g, 10 mmol) or **2b** (1.36 g, 10 mmol) is stirred for 24 h, and the residue is purified by CC (benzene: diethyl ether = 8:2).

Yield: 1.52/1.41 g (81/75%); deep red crystals; m.p.: 160–162°C (benzene/petroleum ether); IR: $\nu = 2221$ (CN) cm^{-1}; ^1H NMR (400 MHz): $\delta = 2.20$ (s, 3H, CH_3), 3.20 (s, 6H, $N(CH_3)_2$), 6.51 (d, $J = 12.2$ Hz, 1H, 4-H), 6.90 (s, 1H, 6-H), 7.82 (d, $J = 12.6$ Hz, 1H, 3=H) ppm; MS: $m/z = 188$ (100%, M^+).

2-Cyano-5-ethyl-6-(N′,N′-dimethylhydrazono)-hexa-2,4-dienenitrile (**3c**; $C_{11}H_{14}N_4$)

A mixture of **1c** (1.26 g, 10 mmol) and **2a** (2.0 g, 10 mmol) is stirred for 48 h, and the residue is purified by CC (*n*-hexane: ethyl acetate = 10:1).

Yield: 900 mg (45%); red crystals; m.p.: 130–131°C (*n*-hexane); IR: $\nu = 2208$ (CN) cm^{-1}; ^1H NMR (80 MHz): $\delta = 1.10$ (t, $J = 7$ Hz, 3H, CH_3), 2.57 (q, $J = 7$ Hz, 2H, CH_2), 3.18 (s, 6H, $N(CH_3)_2$), 6.35 (d, $J = 13$ Hz, 1H, 4-H), 6.75 (s, 1H, 6-H), 7.75 (d, $J = 13$ Hz, 1H, 3-H) ppm; MS: $m/z = 202$ (100%, M^+).

5-Butyl-2-cyano-6-(N′,N′-dimethylhydrazono)-hexa-2,4-dienenitrile (**3d**; $C_{13}H_{18}N_4$)

A mixture of **1d** (1.54 g, 10 mmol) and **2a** (2.0 g, 10 mmol) is stirred for 120 h, and the residue is purified by CC (toluene: diethyl ether = 8:2).

Yield: 960 mg (42%); red crystalline solid; m.p.: 96–98°C (*n*-hexane); IR: $\nu = 2219$ (CN) cm^{-1}; ^1H NMR (250 MHz): $\delta = 0.9$ (m, 3H, CH_3) 1.5 (m, 4H, 2 CH_2), 2.7 (m, 2H, CH_2), 3.20 (s, 6H, $N(CH_3)_2$), 6.50 (d, $J = 10$ Hz, 1H, 4-H), 6.82 (s, 1H, 6-H), 7.8 (d, $J = 10$ Hz, 1H, 3-H) ppm; MS: $m/z = 230$ (100%, M^+).

2-Cyano-5-methyl-6-oxohexa-2,4-dienenitrile (**4**; $C_8H_6N_2O$)

At room temperature, hydrazone **3b** (380 mg, 2 mmol) is dissolved in diluted (1:1) hydrochloric acid 400 cm^3). After 3 h the solution is extracted with CH_2Cl_2 (4×50 cm^3). The combined organic extracts are washed with water, $NaHCO_3$ solution, and water, dried ($MgSO_4$), evaporated *in vacuo*, and the residue is purified by preparative TLC (silica gel, CH_2Cl_2: cyclohexane = 5:1).

Yield: 90 mg (31%); yellowish crystals; m.p.: 101–103°C (petroleum ether); IR: $\nu = 3060$, 2857 (CH), 2233 (CN), 1692 (C=O), 1621 (C=C) cm^{-1}; ^1H NMR (200 MHz): $\delta = 2.09$ (d, $J = 1.6$ Hz, 3H, CH_3), 7.28 (dq, $J = 11.8$ Hz, 1.5 Hz. 1H, 4-H), 7.96 (d, $J = 11.9$ Hz, 1H, 3-H), 9.71 (s, 1H, 6-H) ppm; UV (MeOH): $\lambda_{max} = 297$ nm ($\varepsilon_{max} = 24800$).

Acknowledgments

Financial support provided by the *Fonds der Chemischen Industrie*, Frankfurt, and *Novartis* AG, Basel, is gratefully acknowledged. *R.M. Shaker* thanks the Egyptian Government, and *C. Orlewska* thanks the DAAD for study grants. We are also very grateful to Dr. *P. Sowinski*, Technical University of Gdansk, for recording and discussing the ^1H-^{15}N NMR spectra.

References

[1] Dees M, Otto H-H (1998) Monatsh Chem **129**: 689

[2] Tietze LF, Kettschau G (1997) In: Metz P (ed) Stereoselective Heterocyclic Synthesis I. Springer, Berlin Heidelberg New York, pp 1–120; Ghosez L, Serckx-Poncin B, Rivera M, Bayard P, Sainte F, Demoulin A, Frisque-Hesbain A-M, Mockel A, Munoz L, Bernard-Henriet C (1985) J Heterocycl Chem Suppl Issue **22**: 69

[3] Villacampa M, Perez JM, Avendano C, Menedez JC (1994) Tetrahedron **33**: 10047; Levesque S, Brassard P (1994) Heterocycles **38**: 2205; Koldobskii AB, Lunin W, Voznesenskii SA (1992) Zh Org Khin **28**: 809; Chem Abstr (1993) **118**: 38799k; Koldobskii AB, Lunin W (1991) ibid **27**: 533; (1991) J Org Chem USSR 462; Potts KT, Bhattacharjee D, Walsh EB (1984) J Chem Soc Chem Commun 114; Potts KT, Bhattacharjee D, Walsh EB (1987) J Org Chem **52**: 2285; Gesto C, de la Cuesta E, Avendaño C (1989) Tetrahedron **45**: 4477; Gesto C, de la Cuesta E, Avendaño C (1992) J Pharm Sci **81**: 815; Tamura Y, Tsugoshi T, Mohri SI, Nakajima Y, Kita Y (1985) Chem Pharm Bull **33**: 3257; Waldner A (1987) Eur Pat Appl Ep 221, 023 (Cl. C 07 D 213/84), 06 May; (1985) CH Appl 85/4, 609, 25 Oct. 15 pp; Chem Abstr (1987) **107**: 134210e; Waldner A, Roloff A, Bellus D (1985) Eur Pat Appl Ep 161, 221 (Cl. C 07 D 213/79), 13 Nov; (1984) CH Appl 84/2, 337, 11 May, 29 pp; Chem Abstr (1986) **104**: 207246w; Waldner A (1988) Helv Chim Acta **71**: 486; 493; Waldner A (1989) ibid **72**: 1435; Waldner A (1989) Tetrahedron Lett **30**: 3061

[4] See ref. [1] and literature cited therein

[5] Fleury J-P, Libis B (1964) Bull Soc Chim Fr 413

[6] Pretsch, Clerc, Seibl, Simon (1976) Tabellen zur Strukturaufklärung organ. Verbindungen. Springer, Berlin Heidelberg New York, p H215

[7] Tamura Y, Tsugoshi T, Nakjima Y, Kita Y (1984) Synthesis 930; Ioffe BV, ZC Ienin KN (1961) Dokl Akad Nauk SSSR **141**: 1369; Chem Abstr (1962) **56**: 14038b; Bengoa EG, Echavaren AM (1991) J Org Chem **56**: 3497

Received March 9, 2000. Accepted March 20, 2000