Monatshefte für Chemie 128, 697–700 (1997)

Monatshefte für Chemie
Chemical Monthly

On the Reaction Between Alkyl Isocyanides and 3-Benzylidene-2,4-pentanedione. A Convenient Synthetic Route to Densely Functionalized Furans

I. Yavari*, **A. Shaabani,** and **M. T. Maghsoodlou**

Chemistry Department, Tarbiat Modarres University, Tehran, Iran

Summary. Alkyl isocyanides undergo a formal [1 + 4] cycloaddition reaction with 3-benzylidene-2,4-pentanedione yielding multiply functionalized furan ring systems in fairly high yields. The ^1H NMR spectrum of 4-acetyl -2-(*N*-benzylamino)-5-methyl-3-phenylfuran shows an AB pattern for the benzylic methylene protons as a result of a restricted rotation about the bond between the acetyl group and the furan ring, thus giving rise to perpendicular disymmetric planes.

Keywords. Alkyl isocyanides; [1 + 4] Cycloaddition; Conformational enantiomers; Functionalized furan.

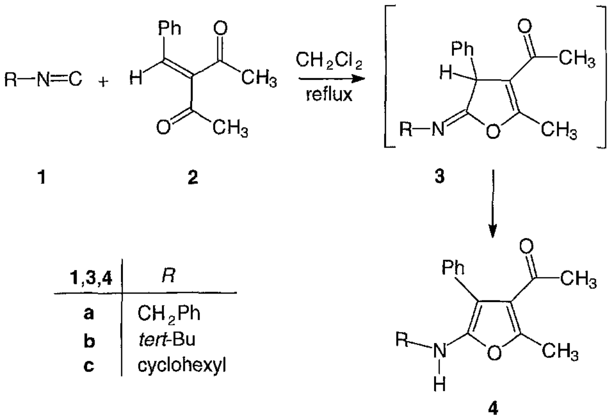
Eine einfache Synthese von hochfunktionalisierten Furanen durch Reaktion von Alkylisocyaniden mit 3-Benzyliden-2,4-pentadion

Zusammenfassung. Alkylisocyanide gehen mit 3-Benzyliden-2,4-pentadion eine formale [1 + 4]-Cycloaddition ein, die in relativ hohen Ausbeuten zu mehrfach funktionalisierten Furansystemen führt. Das ^1H-NMR-Spektrum von 4-Acetyl-2-(N-benzylamino)-5-methyl-3-phenylfuran zeigt für die benzylischen Methylenprotonen ein AB-System, da das Molekül durch die sterische Hinderung der Rotation der Acetylgruppe asymmetrisch wird.

Introduction

Isocyanides [1–4] undergo a formal [1 + 4] cycloaddition reaction with conjugated electrophilic heterodienes. These reactions are of interest for the synthesis of functionalized heterocyclic five-membered ring systems. Cycloadditions of isocyanides with azadienes [5], diazadienes [6], *N*-acylimines [7], α,β-unsaturated esters [8], enones [9], and nitroalkenes [10] have been described.

We report herein that alkyl isocyanides (**1**) undergo smoothly a formal [1 + 4] cycloaddition reaction with 3-benzylidene-2,4-pentanedione (**2**) [11], yielding *N*-substituted 4-acetyl-2-alkylamino-5-methyl-3-phenyl furans (**4**).



1,3,4	*R*
a	CH_2Ph
b	*tert*-Bu
c	cyclohexyl

Scheme 1

Results and Discussion

Structure **4** was assigned to the isolated cycloadducts on the basis of their elemental analyses as well as their IR, ^1H NMR, ^{13}C NMR, and mass spectral data. IR spectroscopy was applied to distinguish structure **4** from the primary cycloadduct, iminolactone **3**, which apparently isomerizes to produce the aromatic furan ring system under the given reaction conditions. Thus, the IR spectra of the isolated products showed strong NH stretching bands at about 3300 cm^{-1}. Further evidence was obtained from proton coupled ^{13}C NMR spectra which showed no methine carbon resonance below 100 ppm. Structure **4** was further confirmed by ^1H NMR spectra that revealed, in each case, a fairly broad singlet in the region of $\delta = 3.6-3.9$ ppm which readily disappeared upon addition of D_2O.

The mass spectra of the crystalline cycloadducts **4** are similar, as expected, and confirm their molecular weights. The very weak molecular ion peak is accompanied by a stronger M+1 peak due to protonation of the furan molecules in the mass spectrometer.

The four quaternery carbon atoms of the furan ring exhibit very different chemical shifts. C-2 and C-5 appear at $\delta = 176$ and 149 ppm, respectively. The signal at about $\delta = 140$ ppm is assigned to C-4, and the high-field signal at about $\delta = 90$ ppm is assigned to C-3. The latter chemical shift is very similar to those reported for the C-3 atom of furan rings bearing electron releasing substituents in position 2 [12]. The proton coupled ^{13}C NMR spectrum of **4c** shows three-bond carbon-hydrogen coupling between C-3 and its vicinal protons on the benzene moiety. Thus, C-3 appears as a triplet with $^3J_{CH} = 3.7$ Hz.

The most noteworthy feature of the ^1H NMR spectrum of **4a** is the AB pattern of the benzylic methylene protons: $\delta_A = 4.54$ ppm, $\delta_B = 4.76$ ppm, $J_{AB} = 15.7$ Hz. The only reasonable source of asymmetry in **4a** that is sufficiently persistent to give rise to diastereotopic protons is a torsional chirality of the molecular skeleton as a result of restricted rotation about the bond between the acetyl group and the furan ring, thus giving rise to perpendicular disymmetric planes [13–15].

We have studied the temperature dependence of the AB quartet in **4a** at 90 MHz in 1,2-dichlorobenzene. Although the relative chemical shifts of the AB proton decrease with increasing temperature, a fairly broad AB quartet was still visible at 170°C, the highest temperature investigated. The observed line widths for the AB quartet of **4a** at 170°C was *ca.* 4.5 Hz, and this leads to a minimum free-energy barrier [16] of $\approx$ 25 kcal·mol^{-1} for the racemization in compound **4a**. If entropy effects are small and can be neglected, the average lifetime before conformational racemisation of **4a** should be more than a day at 20°C [17]. The rate of racemization of **4b** and **4c** should be closely similar to that of **4a**. Thus, compounds **4a**, **4b**, and **4c** potentially can be resolved into optically active forms at room temperature. Attempts to separate the two conformational enantiomers (atropisomers) of **4** are in progress.

Experimental

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were recorded as KBr discs on a Shimadzu-460 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained at 90 MHz and 22.4 MHz, respectively, on a JEOL EX-90 instrument with $CDCl_3$ as solvent and Me_4Si as internal standard. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-rapid analyzer. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides (**1**) were obtained from Aldrich Chemical Company and were used without further purification. The synthesis of 3-benzylidene-2,4-pentanedione (**2**) was carried out as described in the literature [11].

General procedure for the preparation of N-substituted 4-acetyl-2-amino-5-methyl-3-phenylfurans (4)

To a magnetically stirred solution of 3-benzylidene-2,4-pentanedione (376 mg, 2 mmol) in dichloromethane (5 ml), a mixture of alkyl isocyanide (2 mmol) in dichloromethane (2 ml) was added dropwise at 0°C over 5 min. The reaction mixture was then allowed to warm up to 20°C and refluxed for 5 h. After 24 h in a refrigerator at 5°C, crystals of the product were collected by filtration and recrystallized from diethyl ether/hexane (1:1).

4-Acetyl-2-(N-benzylamino)-5-methyl-3-phenylfuran (**4a**)

Yield: 73%; m.p.: 124–126°C; $C_{20}H_{19}O_2N$ (305.38); calc.: C 78.66, H 6.27, N 4.49; found: C 78.5, H 6.1, N 4.4; ν_{max} = 3250 (N-H), 1696 (C=O), 1648 (C=C) cm^{-1}δ_H = 1.62 and 2.13 (2s, 6H, $2CH_3$), 3.58 (br s, 1H, N-H), 4.54, 4.76 (AB system, J = 15.7 Hz, 2H, CH_2), 7.1–7.5 (m, 10H, $2C_6H_5$) ppm; δ_c = 24.35 (CH_3), 30.74 (CH_3), 42.47 (CH_2), 89.02 (C-3), 127.33 (CH), 128.07 (2CH), 128.47 (2CH), 128.55 (2CH), 129.53 (2CH), 129.74 (C), 129.98 (CH), 137.92 (C), 138.98 (C-4), 149.53 (C-5), 167.65 (C-2), 199.82 (C=O) ppm; MS (EI): *m/z* (relative intensity) = 306 (MH^+) (5), 305 (M^+) (2), 215 (M^+-PhNCO) (2), 145 ($C_{10}H_9O$) (10), 91 ($PhCH_2$) (100), 43 (CH_3CO) (52), 42 (CNO) (2).

4-Acetyl-2-(N-tert-butylamino)-5-methyl-3-phenylfuran (**4b**)

Yield: 70%; m.p.: 125–127°C; $C_{17}H_{21}O_2N$ (271.36); calc.: C 75.24, H 7.80, N 5.16; found: C 75.4, H 7.4, N 5.3; ν_{max} = 3390 (N-H), 1685 (C=O), 1645 (C=C) cm^{-1}; δ_H = 1.60 (s, 9H, CMe_3), 1.85 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.9 (br s, 1H, NH), 7.2–7.5 (m, 5H, C_6H_5) ppm; δ_C = 26.43 (CH_3), 28.91 ($3CH_3$), 30.87 (CH_3), 57.01 (CMe_3), 91.34 (C-3), 128.24 (2CH), 129.57 (2CH), 129.74 (CH), 131.442 (C), 148.52 (C-5), 167.81 (C-2), 200.35 (C=O) ppm; MS (EI): *m/z* (relative intensity) = 272 (MH^+) (11), 271 (M^+) (1), 215 (M^+-CMe_3) (15), 173 (M^+-Me_3CNCO) (2), 145 ($C_{10}H_9O$) (34), 77 (C_6H_5) (19), 43 (CH_3CO) (100), 42 (CNO) (10).

4-Acetyl-2-(N-cyclohexylamino)-5-methyl-3-phenylfuran (**4c**)

Yield: 76%; m.p.: 144–146°C; $C_{19}H_{23}O_2N$ (297.38); calc.: C 76.73, H 7.80, N 4.71; found: C 76.1, H 7.4, N 4.4; $\nu_{max} = 3275$ (N-H), 1686 (C=O), 1641 (C=C) cm^{-1}; $\delta_H = 1.2 - 2.3$ (m, 10H, 5 CH_2),1.78 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.41 (tt, 1H, J = 11.7 Hz, 2.7 Hz, CH-N), 3.60 (br s, 1H, NH), 7.2–7.5 (m, 5H, C_6H_5) ppm; $\delta_C = 23.82$ (CH_3), 25.15 (CH_2), 26.27 ($2CH_2$), 29.90 (2 CH_2), 30.74 (CH_3), 52.29 (CH–N), 89.30 (C-3), 128.35 (2CH), 129.49 (2CH), 129.65 (CH), 129.90 (C), 139.71 (C-4), 149.08 (C-5), 166.39 (C-2), 199.86 (C=O) ppm; MS (EI): *m/z* (relative intensity) = 298 (MH^+) (13), 297 (M^+) (2), 215 (M^+-C_6H_{11}) (20), 173 (M^+-$C_6H_{11}NCO$) (5), 145 ($C_{10}H_9O$) (32), 83 (C_6H_{11}) (2), 43 (CH_3CO) (100), 42 (CNO) (8).

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the Tarbiat Modarres University.

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Received January 31, 1997. Accepted February 17, 1997