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Dynamic ^{1}H NMR Study of Aryl-Nitrogen Single Bond and Carbon-Carbon Double Bond Rotational Energy Barriers in Two Highly Functionalized Pyranopyrimidines

Issa Yavari[1,*], **Norollah Hazeri**[2], **Malek T. Maghsoodlou**[3], and **Nader Zabarjad-Shiraz**[1]

[1] Department of Chemistry, University of Tarbiat Modarres, Tehran, Iran
[2] Department of Chemistry, University of Shahid Beheshti, Tehran, Iran
[3] Department of Chemistry, University of Sistan and Baluchestan, Zahedan, Iran

Summary. The reactive 1:1 intermediate produced in the reaction between 2,6-dimethylphenyl isocyanide and dimethyl acetylenedicarboxylate was trapped by N,N′-dimethylbarbituric acid to yield the isomeric products dimethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-4*H*-pyrano[3,2-*d*]pyrimidine-5,6-dicarboxylate and dimethyl (*E*)-2-((2,6-dimethylphenylamino)-(1,3-dimethyl-2,4,6-trioxo-pyrimidine-5-ylidene)-methyl)-but-2-enedioate in a nearly 1:1 ratio and an overall yield of 85%. Dynamic effects were observed in the ^{1}H NMR spectra of these compounds and were attributed to restricted rotation around the aryl-nitrogen single bonds and the polarized carbon-carbon double bond.

Keywords. Restricted rotation; Enaminones; Polarized double bond; CH-Acids.

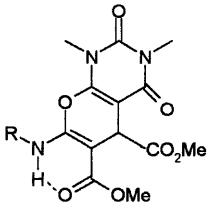
Introduction

We have recently described [1] the synthesis of 4*H*-pyrano[3,2-*d*]pyrimidine derivatives (**1**) from the reaction of alkyl isocyanides [2] with dimethyl acetylenedicaboxylate (*DMAD*) and N,N′-dimethylbarbituric acid. To prepare pyranopyrimidines with an arylamino group at C-7, such as **2**, we now performed the reaction of 2,6-dimethylphenyl isocyanide with *DMAD* and N,N′-dimethylbarbituric acid.

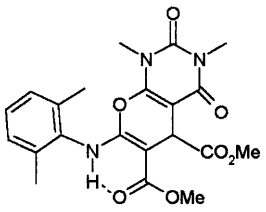
Results and Discussion

The reaction of 2,6-dimethylphenyl isocyanide with *DMAD* in the presence of N,N′-dimethylbarbituric acid afforded the isomeric products dimethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-4*H*-pyrano[3,2-*d*]pyrimidine-5,6-dicarboxylate (**2**) and dimethyl (*E*)-2-((2,6-dimethylphenylamino)-(1,3-dimethyl-2,4,6-trioxo-pyrimidine-5-ylidene)-methyl)-but-2-enedioate (**3**) in a nearly 1:1 ratio and an

* Corresponding author

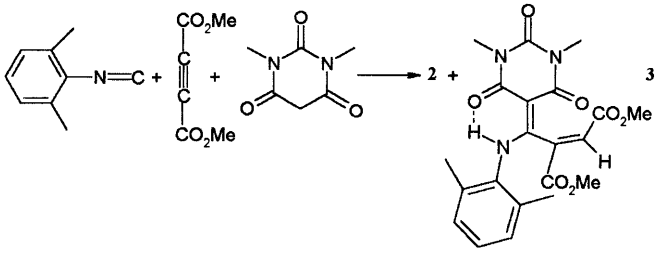


1 (R = alkyl)



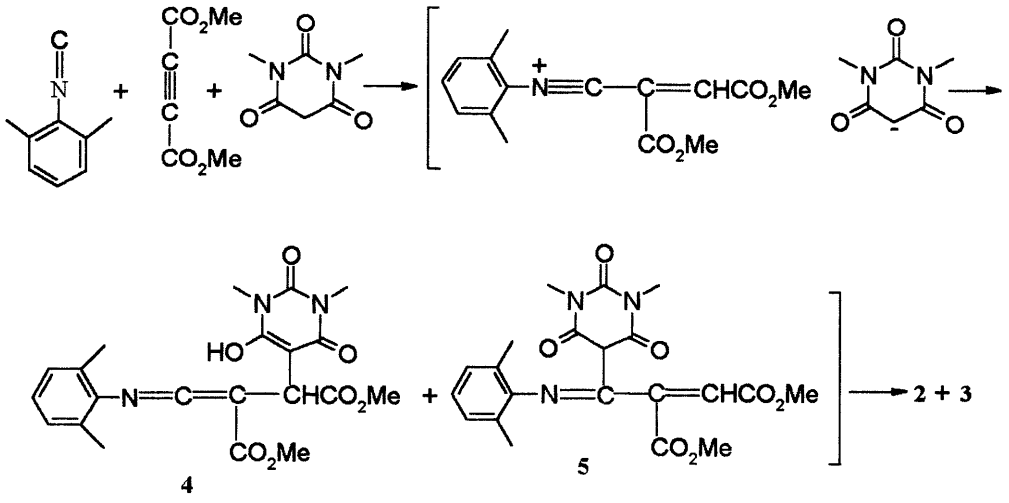
2

overall yield of 85%. The structures of **2** and **3** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these isomeric compounds are fairly similar and display molecular ion peaks, any initial fragmentation involving the loss of the ester moieties. The ^{1}H and ^{13}C NMR data for compounds **2** and **3** are given in the experimental part. The ^{1}H NMR spectrum of **2** exhibits seven sharp singuletts arising from C-methyl ($\delta = 2.20$ and 2.42 ppm), N-methyl ($\delta = 2.85$ and 3.38 ppm), methoxy ($\delta = 3.75$ and 3.85 ppm), and methine ($\delta = 4.76$ ppm) protons, along with a fairly complex multiplet in the aromatic region. The NH group exhibits a broad band at $\delta = 9.8$ ppm, indicating intramolecular hydrogen bond formation with the vicinal carbonyl group. The presence of two separate signals for the C-Me groups in both ^{1}H and ^{13}C NMR spectra of **2** can be explained in term of restricted rotation around the N-aryl bond.



Although we have not yet established the mechanism of the reaction between 2,6-dimethylphenyl isocyanide and *DMAD* in the presence of N,N′-dimethylbarbituric acid in an experimental manner, a possible explanation is proposed in Scheme 1. On the basis of the well established chemistry of isocyanides [2] it is reasonable to assume that **2** and **3** result from an initial addition of the aryl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by N,N′-dimethylbarbituric acid. Then, the positively charged ion might be attacked by the enolate anion of the CH-acid in two ways. The first, which is a *Micheal* addition, leads to the keteneimine **4**. Such an addition product may isomerize under the reaction conditions employed to produce the fused heterocyclic system **2**. The second, which involves direct addition of the enolate anion to the positive ion, produces the heterodiene **5**. This addition product undergoes an imine-to-enamine tautomerism to generate the enaminone system **3** (see Scheme 1). The (*E*)-cofiguration of the carbon-carbon double bond in **3** is based on the chemical shift of the olefinic proton [3].

The ^{1}H NMR spectrum of **2** in 1,2-dichlorobenzene at 50°C showed that the resonances arising from the C-Me protons are appreciably broadened when compared to the corresponding signals in the spectrum measured at room temperature,



Scheme 1

whereas the N-Me and methoxy resonances remain unchanged. The C-Me protons coalesce near 70°C and appear as a fairly sharp symmetrical resonance at 100°C. No further dynamic NMR effects were observed up to 190°C, the highest temperature investigated.

Although no extensive line-shape analysis for **2** was undertaken, the variable temperature spectra allowed to calculate the free energy barrier for the restricted N-aryl bond rotation [4] in **2**. From the coalescence of the N-Me proton resonances and using the expression $k = \pi\Delta\nu/\sqrt{2}$, we calculated the first-order rate constant (k) for the N-aryl bond rotation in **2** to $40\,s^{-1}$ at 70°C (see Table 1). Application of the absolute rate theory with a transmission coefficient of 1 gave a free-energy of activation ($\Delta G^{\neq}$) of $73.9 \pm 2\,kJ \cdot mol^{-1}$, where all known sources of errors were estimated and included [5]. The experimental data available were not suitable for obtaining meaningful values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ were not large [6].

The ^1H NMR spectrum of **3** in 1,2-dichlorobenzene solution at ambient temperature displayed six sharp singlets for the methyl groups: two due to C-Me protons at $\delta = 2.16$ and 2.27 ppm, two for the N-Me groups at $\delta = 3.28$ and

Table 1. Selected proton chemical shifts and activation parameters for **2** and **3** in 1,2-dichlorobenzene

	T/°C	C-Me δ/ppm	N-Me δ/ppm	$\Delta\nu$/Hz	k/s^{-1}	T_c/K	$\Delta G^{\neq}/kJ \cdot mol^{-1}$
2	20	2.22 2.32	2.80 3.35	42	93	358	74.6
	100	2.28	2.81 3.35	–	–	–	–
3	20	2.16 2.27	3.28 3.43	10	22	331	72.8
	80	2.22	3.27 3.42	14	30	450	101.9
	190	2.23	3.35	–	–	–	–

3.43 ppm, and two for the methoxy groups at $\delta = 3.52$ and 3.75 ppm. At about 40°C, the resonances arising from the C-Me protons were appreciably broadened when compared to the corresponding signals at room temperature, whereas the N-Me and methoxy resonances remained unchanged. The C-Me protons coalesced near 58°C and appeared as a fairly broad symmetrical line at 80°C; at this temperature, the N-Me resonances are slightly broadened, and the methoxy bands are sharp. Increasing the temperature to 177°C resulted in the coalescence of the two N-Me resonances; a broad symmetrical signal was observed at 190°C, the highest temperature investigated. The ^{1}H NMR spectra of **3** obtained from 20°C to 190°C clearly showed two distinct dynamic NMR effects. The lower-energy $(72.8\,\mathrm{kJ \cdot mol^{-1}})$ process which led to the coalescence of the two C-Me groups was attributed to the restricted rotation about the N-aryl bond. The higher-energy $(101.9 \pm 2\,\mathrm{kJ \cdot mol^{-1}})$ process which led to the coalescence of the two N-Me signals at 177°C, is supposed to be due to restricted rotation about the highly polarized carbon-carbon double bond of the enaminone moiety in **3** (see Table 1) [7].

In conclusion, the reaction of 2,6-dimethylphenyl isocyanide with electron-deficient acetylenic esters, such as *DMAD*, in the presence of N,N′-dimethylbarbituric acid provides a simple one-pot entry into the synthesis of polyfunctional pyrimidine derivatives of potential interest. Dynamic NMR effects are observed in the ^{1}H NMR spectra of the isomeric products **2** and **3** and are attributed to restricted rotation around the aryl-nitrogen single bond and the polarized carbon-carbon double bond.

Experimental

Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated ones. IR spectra were measured on a Shimadzu IR 460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. 2,6-Dimethylphenyl isocyanide, dimethyl acetylenedicaboxylate, and N,N′-dimethylbarbituric acid were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Preparation of **2** and **3**

To a stirred solution of 0.312 g N,N′-dimethylbarbituric acid (2 mmol) and 0.284 g dimethyl acetylenedicaboxylate (2 mmol) in 10 cm^3 CH_2Cl_2, a mixture of 0.262 g 2,6-dimethylphenyl isocyanide (2 mmol) in 5 cm^3 CH_2Cl_2 was added dropwise at −10°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and to stand for 4 days. The solvent was removed under reduced pressure, and the solid residue was washed with 2×5 cm^3 cold diethyl ether. 0.73 g of the product (85%) were obtained as a yellow powder. The ^{1}H NMR spectrum of the crude product was consistent with the presence of a 1:1 mixture of two isomeric products (see below).

The solid residue was separated by silica (Merck 230–400 mesh) column chromatography using hexane-ethyl acetate mixture as eluent. The first compound was eluted using a 3:1 mixture of hexane-ethyl acetate and was identified as **2**. Elution with a 2:1 mixture of hexane-ethyl acetate gave **3**.

Dimethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-4H-pyrano[3,2-d]pyrimidine-5,6-dicarboxylate (**2**; $C_{21}H_{23}N_3O_7$)

Pale yellow crystals; yield: 0.35 g (41%); m.p.: 180–182°C; IR (KBr): $\nu_{max} = 3205$ (NH), 1720, 1689, 1685, and 1645 (C=O), 1603 (C=C) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 2.20 and 2.42 (6H, 2s, 2 C-Me), 2.85 and 3.38 (6H, 2s, 2 NMe), 3.75 and 3.85 (6H, 2s, 2 OMe), 4.76 (1H, s, CH), 7.1–7.3 (3H, m, arom), 9.8 (1H, br s, NH···O=C) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 18.24 and 18.41 (2 C-*Me*), 28.34 and 28.52 (2 N-Me), 35.67 (CH), 51.59 and 52.65 (2 O-Me), 75.09 and 88.24 (2 *C*=C–O), 127.94, 128.19 and 128.39 (3 CH, arom), 133.73, 135.80 and 136.74 (3 C, arom), 150.22 and 151.56 (2 C=*C*–O), 157.43, 161.09, 169.11 and 173.71 (4 C=O) ppm; MS: *m/z* (%) = 429 (M^+, 46), 370 (100), 338 (55), 310 (50), 284 (76), 224 (32), 59 (39).

Dimethyl (E)-2-((2,6-dimethylphenylamino)-(1,3-dimethyl-2,4,6-trioxo-pyrimidine-5-ylidene)-methyl)-but-enedioate (**3**; $C_{21}H_{23}N_3O_7$)

Yellow crystals; yield: 0.33 g (39%); m.p.: 201–204°C; IR (KBr) $\nu_{max} = 3218$ (NH), 1712, 1707, 1660 and 1643 (C=O), 1609 (C=C) cm^{-1}; ^1H NMR (90 MHz, δ, $CDCl_3$): 2.15 and 2.25 (6H, 2s, 2 CMe), 3.26 and 3.43 (6H, 2s, 2 NMe), 3.54 and 3.76 (6H, 2s, 2 OMe), 6.72 (1H, s, CH), 7.21 (3H, m, arom), 13.70 (1H, br s, NH···O=C) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 18.20 and 18.32 (2 C-*Me*), 27.61 and 27.81 (2 N-Me), 51.96 and 52.72 (2 O-Me), 92.92 (*C*=C–N), 127.94, 127.97, 128.27 and 128.68 (4 CH), 134.05, 134.13, 134.15 and 138.41 (4C), 151.23 (C=*C*–N), 162.19, 162.76, 163.94, 166.10 and 166.75 (5 C=O) ppm; MS: *m/z* (%) = 429 (M^+, 3), 370 (5), 182 (10), 156 (26), 102 (100), 77 (82), 66 (92), 59 (65).

Acknowledgements

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