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On the Reaction between Alkyl Isocyanides and Ethynyl Phenyl Ketone in the Presence of *N*,*N*′-Dimethylbarbituric Acid

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Summary. The reactive 1:1 intermediate produced in the reaction between alkyl isocyanides and ethynyl phenyl ketone was trapped with *N*,*N*′-dimethylbarbituric acid to produce alkyl 1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-5-carboxamides in good yields.

Keywords. Alkyl isocyanides; Ethynyl phenyl ketone; *N*,*N*′-Dimethylbarbituric acid; Pyrimidine derivatives; *Ugi* reaction.

Introduction

Isocyanids, by virtue of their carbenic character, react readily with most common multiple bonds [1–3]. The reaction of isocyanides with carbon-centered triple bonds tends to occur in a stepwise manner and is initiated by a zwitterionic intermediate whose ultimate fate appears to be dictated by the nature of the original triple-bonded substrate [1–4]. These reactions are of interest for the synthesis of functionalized heterocyclic ring systems [5].

We report herein that alkyl isocyanides **1** undergo a smooth addition reaction with ethynyl phenyl ketone in the presence of a strong CH-acid such as *N*,*N*′-dimethylbarbituric acid, yielding alkyl 1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-5-carboxamides (**2**).

Results and Discussion

The reaction of ethynyl phenyl ketone with *tert*-butyl, cyclohexyl, or benzyl isocyanide in the presence of *N*,*N*′-dimethylbarbituric acid afforded alkyl 1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-5-carboxamides (**2**) in overall yields of 68–75%. Compounds **2a**–**c** are stable solids whose structures were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these 1:1:1 adducts are fairly similar and display the expected molecular ion peaks, any initial fragmentation involving the loss of amide and MeNCO moieties. The ^{1}H NMR spectrum of compound **2a** exhibited four

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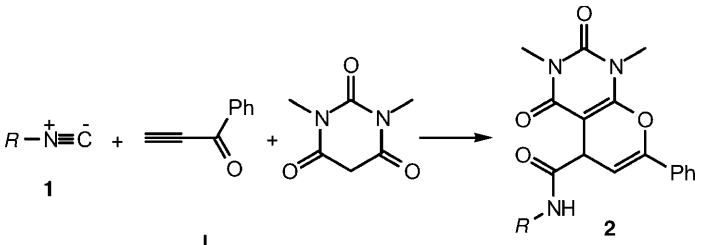
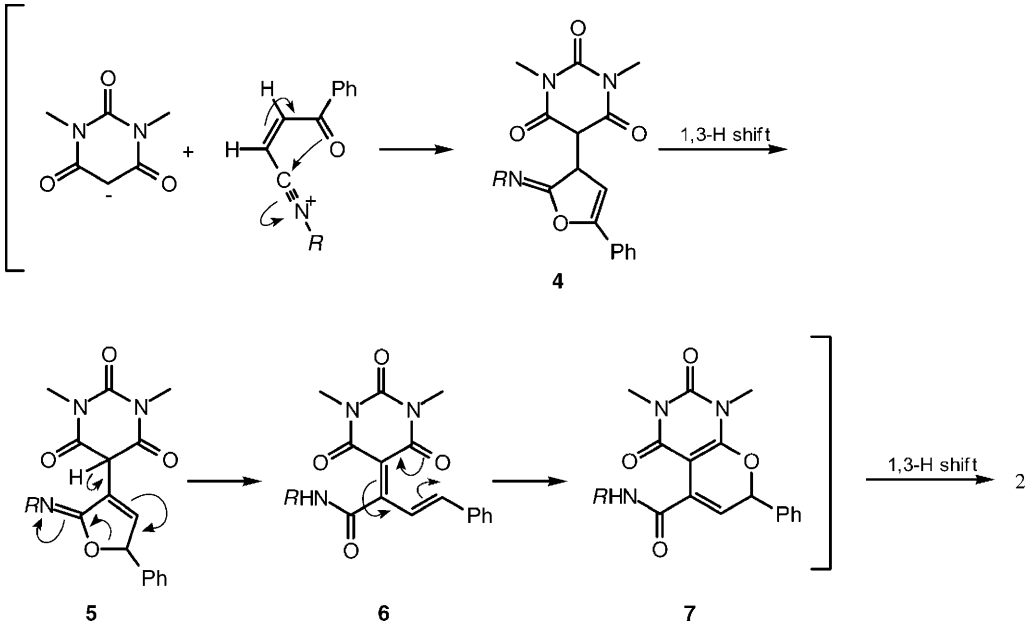


	R	Yield / %
a	*t*-Bu	75
b	Cyclohexyl	70
c	Benzyl	68

Scheme 1

singlets arising from *tert*-butyl ($\delta = 1.35$ ppm), methyl ($\delta = 3.38$ and 3.54 ppm), and NH ($\delta = 6.81$ ppm) protons, along with a fairly complex multiplet in the aromatic region (see Experimental). The methine ($\delta = 4.16$ ppm) and olefinic CH ($\delta =$ 5.74 ppm) protons appear as doublets ($^3J_{HH} = 5$ Hz). The ^{13}C NMR spectrum of **2a** displayed sixteen distinct resonances in agreement with the pyranopyrimidine structure. Partial assignments of these resonances are given in the experimental part. The ^{1}H and ^{13}C NMR spectra of **2b** and **2c** are similar to those of **2a** except for the amido groups, which give rise to characteristic signals with appropriate chemical shifts (see Experimental).

The structural assignment of compounds **2a**–**c** performed on the basis of the ^{1}H and ^{13}C NMR spectra was supported by their IR spectra, the carbonyl region of which displayed three distinct absorption bands for each compound



Scheme 2

(see Experimental). The NH absorption band of compounds **2a–c** appears at about 3270 cm^{-1}.

Although we have not yet established the mechanism of the reaction between alkyl isocyanides and electron deficient ethynyl phenyl ketone in the presence of *N,N′*-dimethylbabituric acid in an experimental manner, a possible explanation is proposed in Scheme 2.

On the basis of the well established chemistry of isocyanides [1–5] it is reasonable to assume that compound **2** results from an initial addition of the alkyl isocyanide to ethynyl phenyl ketone and subsequent protonation of the 1:1 adduct by *N,N′*-dimethylbarbituric acid. Then, the positively charged ion is attacked by the enolate anion of the CH-acid to produce the iminolactone **4**. Such an addition product may isomerize under the reaction conditions employed to dienone **6** which undergoes electrocyclic ring closure and subsequent 1,3-hydrogen shift to give compound **2**. The structure of **2** was distinguished from that of **7** on the basis of the ^{13}C NMR chemical shift of the methine group ($\delta =$ 37.23–38.36 ppm; the methine group in **7** is expected to appear at about 60 ppm).

In conclusion, the reaction of alkyl isocyanides with ethynyl phenyl ketone in the presence of *N,N′*-dimethylbarbituric acid provides a simple one-pot entry into the synthesis of polyfunctional pyranopyrimidine derivatives of potential interest. The present method has the advantage that the reaction is performed under neutral conditions and the substances can be mixed without any activation or modification.

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 results agreed favourably with the calculated values. IR spectra were measured on a Shimadzu IR-460 spectrometer, ^{1}H and ^{13}C NMR spectra with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. Ethynyl phenyl ketone was prepared by addition of ethynylmagnesium bromide to benzaldehyde [6] and subsequent oxidation [7] of the propargylic alcohol. Other chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and used without further purification.

Preparation of **2**

To a magnetically stirred solution of 0.26 g ethynyl phenyl ketone (2 mmol) and 0.32 g *N,N′*-dimethylbarbituric acid (2 mmol) in 20 cm^3 CH_2Cl_2, a mixture of alkyl isocyanide (2 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise at $-5°C$ over 2 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 twice with 10 cm^3 cold diethyl ether.

tert-Butyl-1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5-carboxamide (**3a**; $C_{20}H_{23}N_3O_4$)

White powder; yield: 0.56 g, (75%); m.p.: 182–185°C; IR (KBr): $\nu_{max} = 3355$ (NH), 1701, 1661, 1627 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, δ, $CDCl_3$): 1.35 (9H, s, *t*-Bu), 3.38 (3H, s, NMe), 3.54 (3H, s, NMe), 4.16 (1H, d, $^{3}J_{HH} = 5.0$ Hz, CH), 5.74 (1H, *d*, $^{3}J_{HH} = 5.0$ Hz, CH), 6.81 (1H, s, NH), 7.38–7.60 (5H, m, C_6H_5) ppm; ^{13}C NMR (125.7 MHz, δ, $CDCl_3$): 28.37 (NMe), 28.74 (CMe_3), 29.19 (NMe), 38.36 (CH), 51.39 (N–C), 86.07 (*C*=C–O), 100.21 (*C*H=C–O), 124.76, 128.63, 129.51, 131.81 (aromatic carbons), 148.62, 150.45 (C=*C*–O and HC=*C*–O), 153.75 (NCO), 163.32 (N(2)–CO), 170.45 (NH–CO) ppm; MS: m/z (%) = 370 ($M^+ + 1$, 46), 269 ($M^+ -$ (*t*-Bu)NHCO, 100), 212 (269-MeNCO, 28), 155 (212-MeNCO, 17), 115 (PhCCHCH, 9), 105 (PhCO, 16), 77 (Ph, 12), 57 (MeNCO, 22).

Cyclohexyl-1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5-carboxamide (**3b**; $C_{22}H_{25}N_3O_4$)

White powder; yield: 0.55 g (70%); m.p.: 145–148°C; IR (KBr): $\nu_{max} = 3270$ (NH), 1698, 1694, 1636 (C=O) cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$): 1.20–1.93 (10H, m, CH_2 of C_6H_{11}), 3.38 (3H, s, NMe), 3.55 (3H, s, NMe), 3.73 (1H, m, CH of C_6H_{11}), 4.21 (1H, d, $^3J_{HH} = 4.2$ Hz, CH), 5.76 (1H, *d*, $^3J_{HH} = 4.2$ Hz, CH), 6.81 (1H, s, NH), 7.28–7.60 (5H, m, C_6H_5) ppm; ^{13}C NMR (125.7 MHz, δ, $CDCl_3$): 24.08, 24.13, 25.08, 32.16, 32.41, 48.03 (carbons of C_6H_{11}), 27.87 (NMe), 28.68 (NMe), 37.23 (CH), 85.41 (*C*=C–O), 99.66 (*C*H=C–O), 124.25, 128.16, 129.03, 131.31 (aromatic carbons) 148.08, 149.93 (C=*C*–O and HC=*C*–O), 153.26 (NCO), 162.76 (N(2)–CO), 169.75 (NH–CO) ppm; MS: m/z (%) = 396 ($M^+ + 1$, 27), 269 ($M^+ - C_6H_{11}NHCO$, 100), 212 (269-MeNCO, 28), 155 (212-MeNCO, 17), 115 (PhCCHCH, 11), 105 (PhCO, 26), 77 (Ph, 24).

Benzyl-1,3-dimethyl-2,4-dioxo-7-phenyl-1,3,4,5-tetrahydro-2H-pyrano[2,3-d]pyrimidine-5-carboxamide (**3c**; $C_{23}H_{21}N_3O_4$)

White powder; yield: 0.54 g (68%); m.p.: 157–159°C; IR (KBr): $\nu_{max} = 3270$ (NH), 1691, 1686, 1634 (C=O) cm^{-1}; ^1H NMR (500 MHz, δ, $CDCl_3$): 3.38 (3H, s, NMe) 3.56 (3H, s, NMe), 4.30 (1H, d, $^3J_{HH} = 5.0$ Hz, CH), 4.40 (1H, dd, $^3J_{HH} = 14.9$ Hz, $^3J_{HH} = 5.6$ Hz, CH of CH_2), 4.49 (1H, dd, $^3J_{HH} = 14.9$ Hz, $^3J_{HH} = 6.0$ Hz, CH of CH_2), 5.81 (1H, d, $^3J_{HH} = 5.0$ Hz, CH), 7.22–7.60 (6H, m, NH and C_6H_5) ppm; ^{13}C NMR (125.7 MHz, δ, $CDCl_3$): 28.35 (NMe), 29.19 (NMe), 37.71 (CH), 43.87 (N–C), 85.61 (*C*=C–O), 99.89 (*C*H=C–O), 124.74, 128.69, 129.62, 131.66 (aromatic carbons), 127.33, 128.60, 129.62, 138.23 (aromatic carbons), 148.70, 150.37 (C=*C*–O and HC=*C*–O), 153.87 (NCO), 163.23 (N(2)–CO), 171.24 (NH–CO) ppm; MS: m/z (%) = 404 ($M^+ + 1$, 27), 269 ($M^+ - PhCH_2NHCO$, 100), 212 (269-MeNCO, 28), 155 (212-MeNCO, 15), 115 (PhCCHCH, 10), 105 (PhCO, 26), 91 ($PhCH_2$, 50), 77 (Ph, 27).

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