Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems. The Synthesis of Benzoylamino Substituted 7*H*-Pyrano[2,3-*d*]pyrimidine, 1*H*,6*H*-pyrano-[2,3-*c*]pyrazole and 2*H*-1-benzopyran Derivatives

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Received April 14, 1989

Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) reacts with heterocyclic compounds containing an active methylene group or potential methylene group in the ring system, such as barbituric acid derivatives **1** and **2**, pyrazolones **3** and **4**, and resorcinol, in acetic acid to afford the corresponding benzoylamino substituted pyranopyrimidinones **7** and **8**, pyranopyrazolones **9** and **10**, and 2*H*-1-benzopyranone **11**. The method represents a novel procedure for the preparation of condensed pyranones.

J. Heterocyclic Chem., **26**, 1273 (1989).

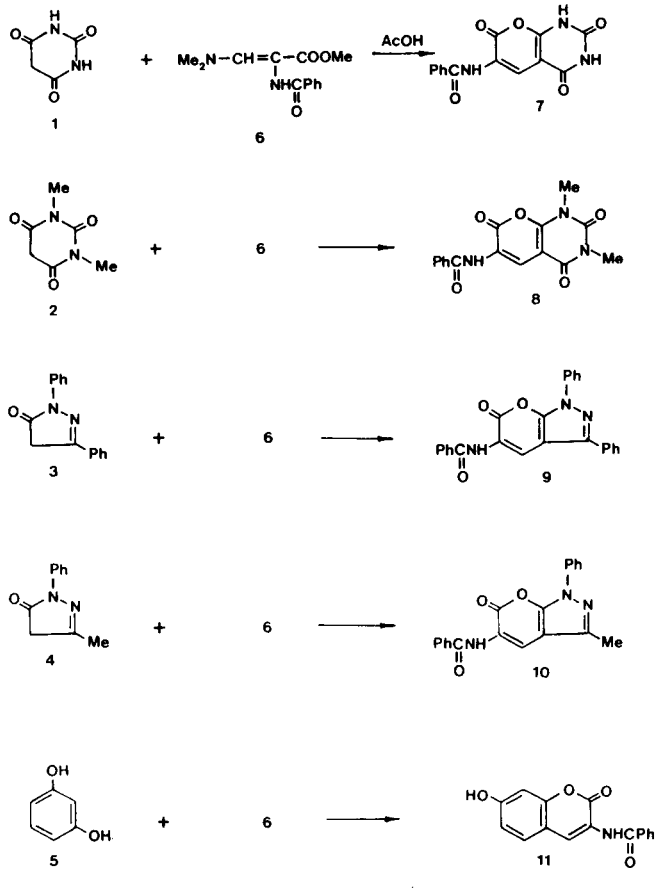
There are numerous methods describing the preparation of 7*H*-pyrano[2.3-*d*]pyrimidine derivatives known in the literature. Most of them are based on barbituric or thiobarbituric acids and their alkylidene or arylidene derivatives. They react with compounds containing an active methylene group under Michael conditions or acetylenes to give in some instances derivatives of 7*H*-pyrano[2,3-*d*]-pyrimidines [1]. Recently, the reaction of cinnamonitriles with barbituric or thiobarbituric acids [2], and a one-step synthesis by treatment of thiobarbituric acid with acetone in the presence of triethylamine [3] have been described. The most common methods for the preparation of pyrano-[2,3-*c*]pyrazole derivatives are cyclocondensations of pyrazolone derivatives with active methylene compounds and aliphatic or aromatic aldehydes [4-12], the reaction of 2-thiocarbamoylcinnamonitriles with active methylene compounds [13] and hydrazides with β-keto esters [1]. Frequently, derivatives of this bicyclic system have been found as by-products in some other reactions [14].

There is a continuous interest in the synthesis of derivatives of these systems, since some of them have been found to be good vasodilators, hypotensive, hypoglycemic [15], antiinflamatory and analgesic agents [9].

Recently, methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) [16,17] has been used for the preparation of 2-benzoylamino-3-(3-indolyl)propenoate [16], methyl 2-benzoylamino-3-heteroarylaminopropenoates [17] and methyl 3-arylamino-2-benzoylaminopropenoates [18] as intermediates in the synthesis of arylaminoalanines [19].

In this communication we report, as a further application of methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) for the preparation of heterocyclic systems, a novel synthesis of some fused 2*H*-pyran-2-ones from cyclic systems containing an active methylene or potential methylene group as a part of the ring system. In this connection, we selected barbituric acid (**1**) its 1,3-dimethyl derivative **2**, 1,3-diphenylpyrazol-5-one (**3**) and 3-methyl-1-phenylpyrazol-5-one (**4**), and resorcinol (**5**). When these compounds are heated with methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) in the presence of acetic acid for

Scheme 1

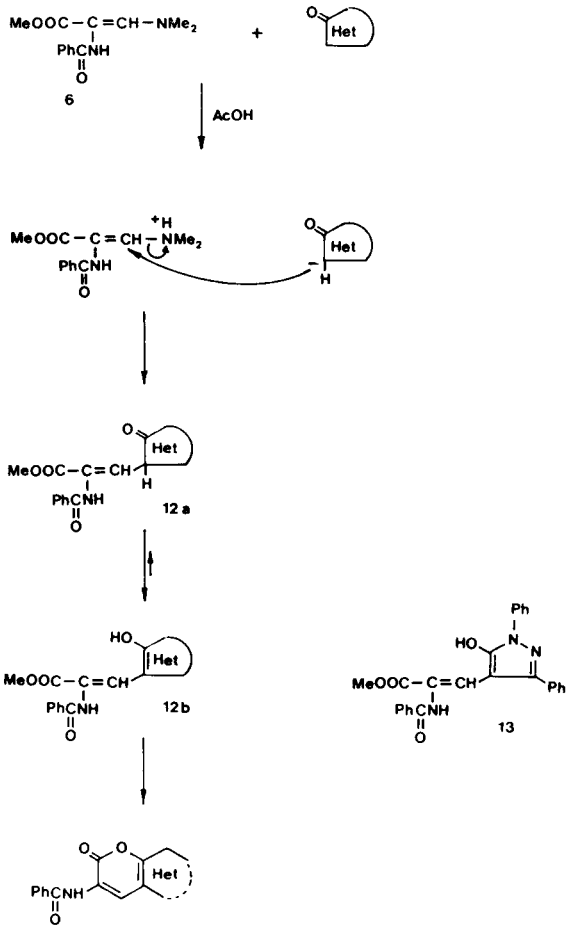


several hours, the corresponding bicyclic systems, derivatives of 7*H*-pyrano[2,3-*d*]pyrimidine **7** and **8**, 1*H*,6*H*-pyrano[2,3-*c*]pyrazole **9** and **10**, and 2*H*-1-benzopyran-2-one **11** with benzoylamino group attached next to the carbonyl group of the pyranone ring, are formed in high yields.

The reaction proceeds as a nucleophilic attack of the anion, formed from a cyclic system, to protonated form of the reagent, in which dimethylamine is eliminated, to give the intermediate, which could exist in two tautomeric forms **12a** and **12b**, followed by cyclization into fused system.

This is supported by the following experiment. When compounds **3** and **6** are heated in acetic acid for 30 minutes the compound **13** was formed and isolated, which cyclized into **9**, when heated in acetic acid for 5 to 6 hours.

Scheme 2



The structure of bicyclic systems were determined on the basis of elemental analyses, ir, ms, and nmr spectra. All compound gave correct elemental analyses and strong molecular ions in mass spectra. The most indicative are the nmr spectra. Namely, the protons at position 5 in the compounds **7** and **8**, and at position 4 in the compounds **9**, **10**, and **11** are shifted downfield and appear at δ = 8.21-8.73 ppm, in agreement with other pyranones and fused pyranones [20], while the corresponding proton in the noncyclized compound **13** appears at δ = 6.63 ppm.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a JEOL JNM 90 Q FT instrument, mass spectra on a Hitachi-Perkin-Elmer RMU-6L, ir spectra on a Perkin-Elmer 727 spectrometer, and microanalyses for C, H, and N on a Perkin-Elmer Analyser 240 C.

The following compounds were prepared according to the procedures described in literature: 1,3-diphenylpyrazol-5-one (**3**) [21], 3-methyl-1-phenylpyrazol-5-one (**4**) [21], and methyl 2-benzoylamino-3-dimethylaminopropenoate (**6**) [17].

6-Benzoylamino-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrano[2,3-*d*]-pyrimidin-7-one (**7**).

A mixture of **1** (0.64 g, 0.005 mole) and **6** (1.24 g, 0.005 mole) in glacial acetic acid (15 ml) was heated under reflux for 6 hours. The precipitate, formed during this time, was, after cooling, collected by filtration and recrystallized from acetic acid to give **7** (1.35 g, 90%), mp >320°; ir (potassium bromide): ν CO = 1740, 1710 cm^{-1}; ms: M$^+$ = 299; ^{1}H nmr (DMSO-d$_6$): δ 7.50-7.59 (m, 3H) and 7.88-7.99 (m, 2H) (PhCO), 8.21 (s, H$_5$), 9.72 (br s, NH), 11.52 (br s, NH).

Anal. Calcd. for $C_{14}H_9N_3O_5$: C, 56.19; H, 3.03; N, 14.04. Found: C, 56.33; H, 3.10; N, 14.13.

In an analogous manner the following compounds were prepared:

6-Benzoylamino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7*H*-pyrano[2.3-*d*]pyrimidin-7-one (**8**).

This compound was prepared from **2** in 83% yield, mp 272-273° (from acetic acid): ir (potassium bromide): ν CO = 1740, 1720 cm^{-1}; ms: M$^+$ = 327; ^{1}H nmr (DMSO-d$_6$): δ 3.27 (s, 1-Me), 3.43 (s, 3-Me), 7.47-7.58 (m, 3H) and 7.86-7.96 (m, 2H) (PhCO), 8.34 (s, H$_5$), 8.9 (br s, NHCO).

Anal. Calcd. for $C_{16}H_{13}N_3O_5$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.56; H, 4.02; N, 12.72.

5-Benzoylamino-1,3-diphenyl-1*H*,6*H*-pyrano[2.3-*c*]pyrazol-6-one (**9**).

This compound was prepared from **3** in 78% yield, mp 237-238° (from acetic acid); ir (potassium bromide): ν CO = 1730, 1690 cm^{-1}; ms: M$^+$ = 407; ^{1}H nmr (DMSO-d$_6$): δ 7.49-7.98 (m, 1-Ph, 3-Ph, PhCO), 8.73 (s, H$_4$), 8.75 (br s, NHCO).

Anal. Calcd. for $C_{25}H_{17}N_3O_3$: C, 73.70; H, 4.21; 10.31. Found: C, 73.46; H, 4.15; N, 10.32.

5-Benzoylamino-3-methyl-1-phenyl-1*H*,6*H*-pyrano[2.3-*c*]pyrazol-6-one (**10**).

This compound was prepared from **4** in 86% yield, mp 165° (from a mixture of toluene and cyclohexane); ir (potassium bromide): ν CO = 1730, 1690 cm^{-1}; ms: M$^+$ = 345; ^{1}H nmr (DMSO-d$_6$): δ 2.41 (s, 3-Me), 7.51-7.96 (m, 1-Ph, PhCO), 8.43 (s, H$_4$), 10.9 (br s, NHCO).

Anal. Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.55; H, 4.38; N, 12.17. Found: C, 69.23; H, 4.47; N, 12.17.

3-Benzoylamino-7-hydroxy-2*H*-1-benzopyran-2-one (**11**).

This compound was prepared from **5** in 73% yield, mp 285-287° (from acetic acid); ir (potassium bromide): ν CO = 1740, 1710 cm^{-1}; ms: M$^+$ = 281; ^{1}H nmr (DMSO-d$_6$): δ 6.87-6.90

(m, H_5, H_6, H_7), 7.54-7.64 (m, 3H) and 7.91-8.02 (m, 2H) (PhCO), 8.47 (s, H_4), 9.55 (br s, 7-OH), 10.48 (br s, NHCO).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.58; H, 3.93; N, 4.96.

Methyl 2-Benzoylamino-3-(5-hydroxy-1,3-diphenylpyrazolyl-4)-propenoate (**13**).

A mixture of **3** (1.18 g, 0.005 mole) and **6** (1.24 g, 0.005 mole) in glacial acetic acid (10 ml) was heated under reflux for 30 minutes. The precipitate, formed after cooling to room temperature, was collected by filtration and recrystallized from a mixture of toluene and cyclohexane to give **13** (1.83 g, 84%), mp 173-175°; ir (potassium bromide): ν CO = 1720, 1680 cm^{-1}; ms: M^+ = 439: ^1H nmr (DMSO-d_6): δ 3.68 (s, OMe), 6.63 (s, CH=C), 7.26-8.02 (m, 1-Ph, 3-Ph, PhCO), 11.9 (br s, NHCO), (OH exchanged).

Anal. Calcd. for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56. Found: C, 70.94; H, 4.90; N, 9.39.

Cyclization of **13** into **9**.

A solution of **13** (878 mg, 0.002 mole) in glacial acetic acid (10 ml) was heated under reflux for 6 hours. The precipitate, formed during this time, was collected by filtration and recrystallized form acetic acid to give **9** (740 mg, 91%), mp 237-238°. The compound is identical with an authentic sample prepared from **3** and **6** as described above.

Acknowledgement.

The authors wish to express their gratitude to the Research Council of Slovenia for partial financial support of this investigation.

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