# Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems. The Synthesis of Substituted 3-Benzoylamino-2*H*-pyran-2-ones

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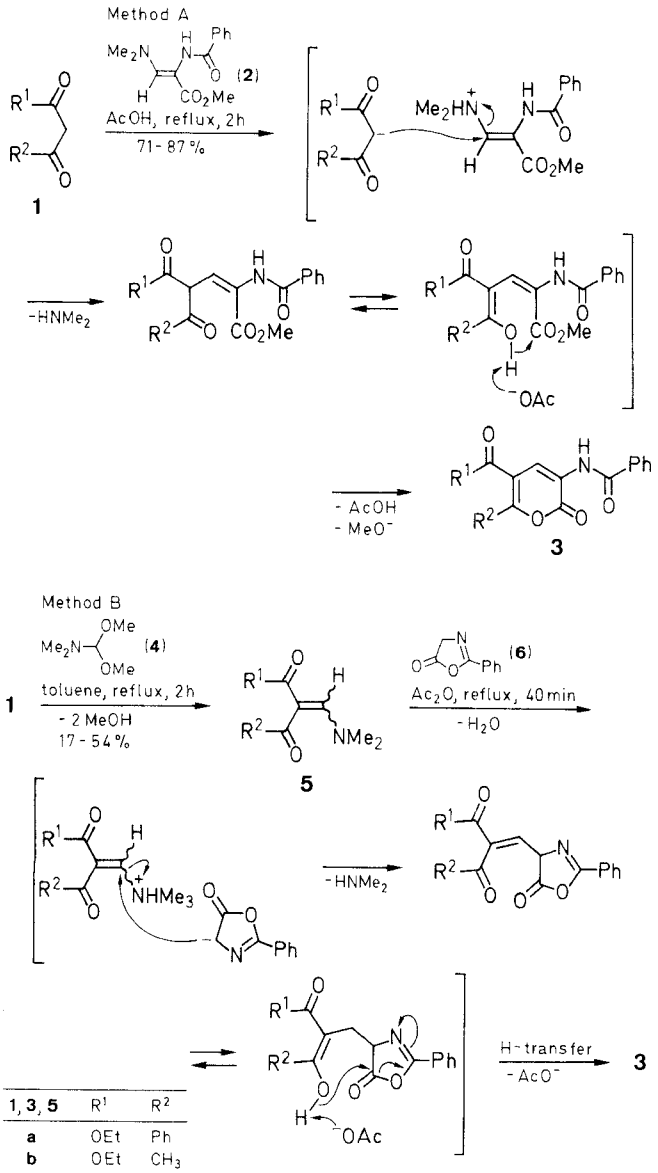
5,6-Disubstituted 3-benzoylamino-2*H*-pyran-2-ones **3** are prepared either from 1,3-dicarbonyl compounds **1** and methyl 2-benzoylamino-3-dimethylaminopropenoate **(2)** in an one-step reaction, or from ethyl 2-acyl-3-dimethylaminopropenoates **5a,b** or 2-(dimethylamino)methylene-1,3-diketones **5c,d** and 5-oxo-2-phenyl-1,3-oxazole **6**.

There are numerous methods of preparation of substituted 2*H*-pyran-2-ones described in literature.[1] Substituted 3-benzoylamino-2*H*-pyran-2-ones have been prepared by reduction of the corresponding nitro derivatives,[2] by condensation of 4-ethoxymethylene-5-oxo-2-phenyl-1,3-oxazole with active methylene compounds[3] or 5-phenylisoxazole,[4] or from 5-oxo-2-phenyl-1,3-oxazole and benzoylacetylenes.[4]

Recently, methyl 2-benzoylamino-3-dimethylaminopropenoate **2**, prepared either in a two-step procedure from hippuric acid by treatment with dimethylformamide and phosphoryl chloride, followed by methanolysis of the oxazolone intermediate,[5] or in an one-step procedure from hippuric acid and dimethylformamide dimethyl acetal (DMFDMA),[6] has been found to be a versatile intermediate for the preparation of methyl 2-benzoylamino-3-(2-indolyl)-propenoates,[5] methyl 2-benzoyl-

amino-3-heteroarylaminopropenoates,[6] and methyl 3-arylamino-2-benzoylaminopropenoates, intermediates in the synthesis of arylaminoalanines.[7]




| 1, 3, 5 | $R^1$ | $R^2$ |
|---|---|---|
| a | OEt | Ph |
| b | OEt | $CH_3$ |
| c | Ph | $CH_3$ |
| d | $CH_3$ | $CH_3$ |

In this communication we report an alternative method for the preparation of substituted 3-benzoylamino-2*H*-pyran-2-ones **3**, in which this reagent can be applied as three-carbon synthon.

β-Keto esters **1a,b** and 1,3-diketones **1c,d** react with methyl 2-benzoylamino-3-dimethylaminopropenoate **(2)** in the presence of acetic acid to afford 5,6-disubstituted 3-benzoylamino-2*H*-pyran-2-ones **3**. The reaction proceeds most probably initially as nucleophilic substitution of the protonated dimethylamino group of the reagent **2** by a carbon nucleophile, followed by cyclization in which methanol is eliminated, producing the final product in high yields, (Method A).

Alternatively, the same compounds can also be obtained from ethyl 2-acyl-3-dimethylaminopropenoates **5a,b** or 2-(dimethylamino)methylene-1,3-diketones **5c,d** prepared *in situ* from the corresponding 1,3-dicarbonyl compounds **1** and DMFDMA,[8-10] and 5-oxo-2-phenyl-1,3-oxazole **(6)**, prepared *in situ* from hippuric acid and acetic anhydride.[11-12] The reaction proceeds first as a nucleophilic substitution of the protonated dimethylamino group of **5** followed by nucleophilic attack of the carbon nucleophile, formed from oxazole **6** in the presence of acetic anhydride, and further cyclization (Method B) (Scheme **A**).

The structures of compounds **3a–d** are supported by IR, $^1$H-NMR spectra and microanalytical data. All compounds show IR spectra NH bands at $\nu$ = 3400–3320 cm$^{-1}$, and carbonyl bands at $\nu$ = 1720–1640 cm$^{-1}$. In the case of unsymmetrically substituted 1,3-diketones, such as **1c**, the compound **3c** is formed regiospecifically as the only product. In this example, $^1$H-NMR spectrum shows two well resolved multiplets at $\delta$ = 7.43–7.63 and $\delta$ = 7.75–7.89 integrating for 3H and 2H, respectively, a pattern typical for a benzoyl group, supperimposed on the identical pattern of the *N*-benzoyl group. This observation excludes the isomeric 5-acetyl-6-phenyl derivative **3** ($R^1$ = MeCO, $R^2$ = Ph).

The methods represent new general syntheses of substituted 3-benzoylamino-2*H*-pyran-2-ones.

**Table.** 5,6-Disubstituted 3-benzoylamino-2H-pyran-2-ones **3** Preparation

| Product | Method | Yield[a] (%) | mp (°C) (solvent) | Molecular Formula[b] or Lit. mp (°C) | IR (KBr)[c] $\nu$(cm$^{-1}$) | $^1$H-NMR ($CDCl_3$/TMS)[d] $\delta$, $J$(Hz) |
|---|---|---|---|---|---|---|
| **3a** | A | 87 | 144–146 | $C_{21}H_{17}NO_5$ | 3360, 1705, | 1.18 (t, 3H, $J$ = 7.2, $OCH_2\underline{CH_3}$), 4.22 (q, 2H, $J$ = 7.2, $OCH_2CH_3$), 7.46–7.62 (m, 8$H_{arom}$), 7.87–7.98 (m, 2$H_{arom}$), 8.66 (br s, 1H, CONH), 8.88 (s, 1H, H-4) |
| | B | 44 | (heptane/ toluene) | (363.4) | 1640 (br) | |
| **3b** | A | 73 | 134–136 | 135–138[3] | 1710, 1700, | 1.40 (t, 3H, $J$ = 7.2, $OCH_2\underline{CH_3}$), 2.68, 3H, H-6), 4.36 (q, 2H, $J$ = 7.2, $OCH_2CH_3$), 7.43–7.63 (m, 3$H_{arom}$), 7.85–7.96 (m, 2$H_{arom}$), 8.55 (br s, 1H, CONH), 8.87 (s, 1H, H-4) |
| | B | 17 | (EtOH) | | 1640 (br) | |
| **3c** | A | 79 | 158–160 | $C_{20}H_{15}NO_4$ | 3390, 1720, | 2.38 (s, 3H, H-6), 7.40–7.61 (m, 6$H_{arom}$), 7.75–7.88 (m, 4$H_{arom}$), 8.50 (s, 1H, H-4), 8.35 (br s, 1H, CONH) |
| | B | 54 | (EtOH) | (333.3) | 1660 (br) | |
| **3d** | A | 71 | 136–138 | 139–140[3] | 3320, 1720, | 2.55 (s, 3H, $COCH_3$), 2.62 (s, 3H, H-6), 7.50–7.64 (m, 3$H_{arom}$), 7.85–7.96 (m, 2$H_{arom}$), 8.61 (br s, 1H, CONH), 8.91 (s, 1H, H-4) |
| | B | 51 | (EtOH) | | 1660 (br) | |

[a] Yield of purified product is given.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.21, N +0.35.
[c] Recorded on a Perkin-Elmer 1310 Infrared spectrophotometer.
[d] Obtained on a Jeol 90 Q FT Spectrometer.

The following compounds were prepared in essentially the same way as reported in literature: methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**),[6] ethyl 2-benzoyl-3-dimethylaminopropenoate (**5a**)[8] and 5-oxo-2-phenyl-1,3-oxazole (**6**).[11,12] The procedure described for **5a** was used also for preparation of ethyl 2-acetyl-3-dimethylaminopropenoate (**5b**), 2-(dimethylamino)methylene-1-phenyl-1,3-butanedione (**5c**), and 3-(dimethylamino)methylene-2,4-pentanedione (**5d**).[9,10]

**5,6-Disubstituted-3-benzoylamino-2*H*-pyran-2-ones (3); General Procedure:**

Method A: A mixture of 1,3-dicarbonyl compound **1** (0.01 mol), methyl 2-benzoylamino-3-dimethylaminopropenoate **2** (2.48 g, 0.01 mol) and acetic acid (20 mL) is heated under reflux for 2 h. The volatile components are then evaporated in vacuo, aq. EtOH (50%, 50 mL) is added and the mixture is left at r.t. until the oily precipitate solidifies. The crystalline product **3** is separated by filtration and recrystallized from an appropriate solvent (Table).

Method B: To a solution of 1,3-dicarbonyl compound **1** (0.01 mol) in toluene (10 mL) DMFDMA (1.5 mL) is added and the mixture is heated under reflux for 2 h. The volatile components are evaporated in vacuo to give **5**. This is dissolved in acetic anhydride (10 mL), hippuric acid (1.8 g, 0.01 mol) is added and the mixture is heated under reflux for 40 min. The volatile components are evaporated in vacuo, aq. EtOH (50%, 50 mL) is added to the residue and the mixture is left at room temperature until the oily precipitate solidifies. The crystalline product **3** is then separated by filtration and recrystallized from an appropriate solvent (Table).

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