A Simple Method for Knoevenagel Condensation of α,β-Conjugated and Aromatic Aldehydes with Barbituric Acid

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Received June 26, 2000

Several aromatic and α,β-conjugated aromatic aldehydes were condensed with barbituric acid in methanol solution in the absence of acid or base as a catalyst, affording 5-ylidenebarbituric acid derivatives in almost quantitative yields.

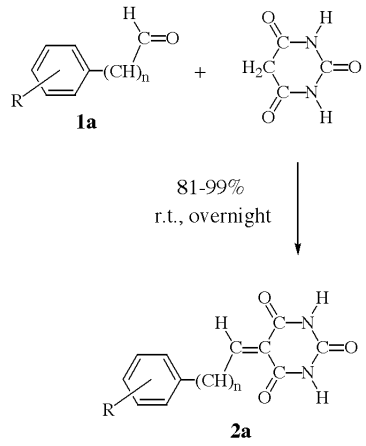
J. Heterocyclic Chem., **38**, 655 (2001).

The derivatives of barbituric acid have a special place in pharmaceutical chemistry. Their biological activities range from classical applications in medical treatments as hypnotic, sedative, and anesthetic drugs [1] to the more recent reports indicating that they have applications in anti-tumor [2], anti-cancer [3], and anti-osteoporosis [4] treatments.

Barbituric acid is a strong acid, having a pK_a = 4.01 in water. It is partially soluble in solvents such as water and methanol in which barbituric acid continue to have strong acidic properties [5]. Barbituric acid also has an "active" methylene group and can be involved in condensation reactions with aldehydes or ketones that do not contain an α-hydrogen. The general type of this reaction is usually called the Knoevenagel condensation [6]. The reaction of barbituric acid with carbonyl compounds was studied as early as 1864. The isolated products contain mono- as well as di-substituted condensation products [7]. The target of every synthetic chemist is to develop a simple procedure that produces the quantitative formation of one product. To achieve formation of only one (mono) condensation product between aromatic aldehydes and barbituric acid, various acid and base catalyzed reactions were used [8-14]. There are some very interesting approaches to obtain high yields in this condensation. For instance, Villemin and Labiad microwaved a mixture of barbituric acid, aromatic aldehyde, and clay (Montmorillonite KSF) without solvent [10]. The product was obtained in high yield after the DMF extraction from the solid reaction mixture. Another interesting approach also performs condensation in the solid state with another clay (Tonsil Actisil FF) and infrared irradiation [15,16].

Here we would like to present an exceptionally simple procedure for performing the Knoevenagel condensation between aromatic and α,β-conjugated aromatic aldehydes with barbituric acid in a methanol solution. Some selected products of this condensation are presented in the Scheme. First of all, the reaction is performed without a base or acid catalyst, excluding the auto-catalyst of the barbituric acid alone. The procedure involves mixing an aldehyde with a barbituric acid in a sufficient amount of methanol to dissolve both of the reactants. Regarding the reactivity of the applied aldehyde, the reaction mixture is left to stir at room temperature for few hours or as long as five days. The completion of the reaction determines the way in which the product is isolated.

The α,β-conjugated aromatic aldehydes, such as *trans*-cinnamaldehyde and *trans*-3-(2-furyl)acrolein, produce a solid precipitate (product) after several minutes. This is also true for electron rich aromatic aldehydes, such as 4-dimethylaminobenzaldehyde, hydroxybenzaldehyde, and indole-3-carbaldehyde. In these cases, the reaction is practically over in several minutes. The product has a very low solubility in cold methanol. Separation of the product from traces of both reactants involves a simple filtration of the reaction mixture followed by washing the crystals with



1a **2a**

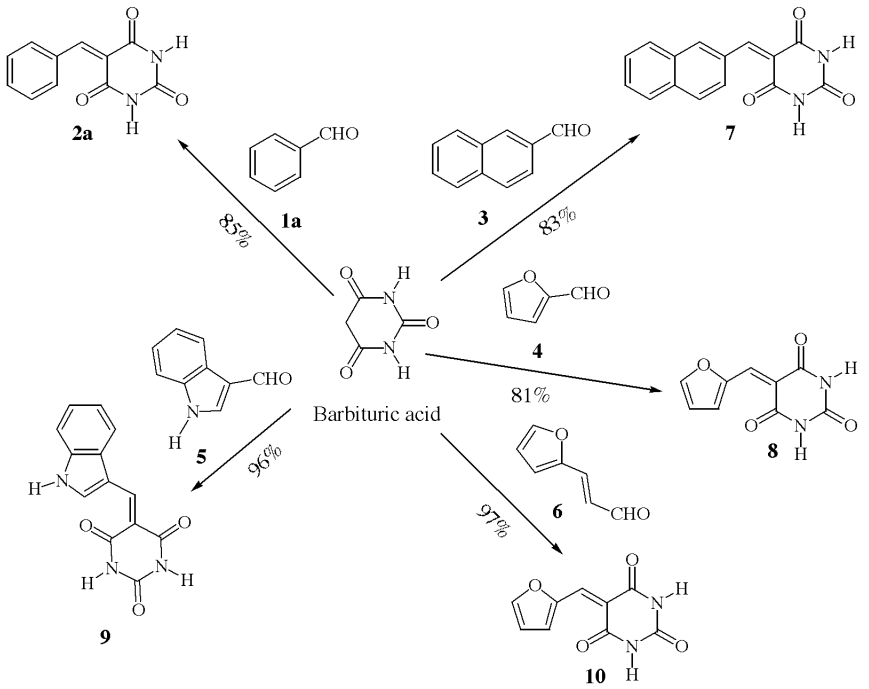
Table

Knoevenagel Reaction Between Various Aromatic and Conjugated Aromatic Aldehydes with Barbituric Acid

Aldehyde	R	n	Procedure	Product	Yield (%) [a,b]
1a	H	0	B	**2a**	85
1b	H	2	A	**2b**	95
1c	*p*-$(CH_3)_2N$	0	A	**2c**	98
1d	*p*-$(CH_3)_2N$	2	A	**2d**	99
1e	*p*-OH	0	A	**2e**	95
1f	*p*-OH	2	**A**	**2f**	98
3			B	**7**	83
4			B	**8**	81
5			A	**9**	96
6			A	**10**	97

[a] Isolated yields; [b]All products have identical ^1H and ^{13}C nmr spectra as authentic samples reported elsewhere [9-16].

Scheme



Several products of the Knoevenagel condensation products with barbituric acid as a source of "active" methylene group.

cold methanol (Method A). In this case, isolated yields of the Knoevenagel product of the condensation are close to quantitative (Table) and the purity is over 99%. All the products of the condensation with barbituric acid are thermally sensitive. They all decompose in the course of melting point determination with decomposition at or over 260 ºC. They are even more thermally sensitive in solution. Therefore, their purification by hot crystallization is not advisable.

To obtain 90% conversion for less reactive aromatic aldehydes, several days stirring of the reaction mixture at room temperature is required [17]. Even if a solid precipitates from the reaction mixture, it contains a mixture of both starting materials. As mentioned above, crystallization of the product from high temperature solvent diminishes the isolation yield considerably. Purification of the product through room temperature crystallization using solvents such as ethyl acetate or petroleum ether slightly improves the purity of the product in regard to the aldehyde, but barbituric acid is hard to separate in this way. The purification procedure must be repeated several times, and yields of the condensation product are modest. The best purification procedure involves evaporation of methanol at reduced pressure and room temperature to a solid residue (Method B). To eliminate barbituric acid, water was added to the solid residue and after stirring at room temperature the remaining solid was separated by filtration. To eliminate the starting aldehyde, the solid was slurred in ether and the resulting suspension was stirred at room temperature for several minutes. After filtration, the crystalline material contains only product of the Knoevenagel condensation (Table).

Unfortunately, as simple as this reaction is, it is only applicable to aromatic aldehydes and α,β-conjugated aromatic aldehydes. Our attempt to use aliphatic aldehydes, such as hexanal, to obtain the corresponding barbituric condensation product was not synthetically successful. Following the reaction by nmr spectroscopy in methanol-d_4 (CD_3OD) as a solvent it is possible to observe the formation of around 5-10% of the condensation product [18]. The reaction conversion stays at that level after several days [19]. If the reaction is carried out for a long time, a trace of other products, such as products of an Aldol condensation was formed. This is also the case when the reaction with ketones was performed. For instance, when acetophenone was used as a source of carbonyl compound it was not possible to detect even a trace of the product in the reaction mixture.

In conclusion, we have described an exceptionally simple room temperature Knoevenagel condensation between aromatic and α,β-conjugated aromatic aldehydes with barbituric acid in methanol without a catalyst. The yield of the condensation is very high and depends on the nature of the aldehyde used. Benzaldehydes with extended conjugation, or with electron-donating substituents will

give the desired product with almost quantitative yields, while benzaldehydes with electron-withdrawing substituents will give little or no product at all. All the reaction manipulations (reaction, separation of the product, and purification of the product) were performed at room temperature. In this way, the decomposition of the thermally sensitive Knoevenagel barbituric acid product is avoided.

EXPERIMENTAL

Melting points were taken on an Electrothermal IA 9000 Digital Melting Point Apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were run on Varian Unity 400 MHz NMR spectrophotometer with DMSO-d6 as a solvent. The J coupling constants are given in ppm. The mass spectra were recorded on a Micromass Quattro 2 Triple Quadrapole Mass Spectrometer; Elementary Analysis was performed by Atlantic Microlab, Inc., Norcross, GA.

Preparation of 5-(4-Dimethylaminobenzylidene)barbituric Acid (**1c**).

Procedure A.

A mixture of barbituric acid (12.8g; 0.1 mol) and 4-dimethylaminobenzaldehyde (14.9g; 0.1 mol) in methanol (500 mL) were stirred at room temperature. After a few minutes the solution became a suspension and the color of crystals changed from yellow to deep red [20]. The suspension continued to stir at room temperature overnight. Solid product was separated by filtration and washed several times with cold methanol (3 x 50 mL). The isolated yield of the red crystalline product was 35.4 g (98%). An analytical sample had mp 277ºC with decomposition; lit. mp 275 ºC with decomposition [9]; IR (potassium bromide) 3095-3080, 1700, 1640, 1500 cm^{-1}; ^{1}H nmr: δ 11.04 (s, 1H, NH), 10.91 (s, 1H, NH); 8.42 (d, J = 0.031, 2H, aromatic-CH), 8.13 (s, 1H, C=CH), 6.78 (d, J = 0.031, 2H, aromatic-CH), 3.11 (s, 6H, $N(CH_3)_2$); ^{13}C nmr: δ 161.2, 159.2, 152.0, 150.7, 146.8, 135.6, 116.5, 107.7, 106.0, and 38.0; ms 259 (M^+, 5), 215 (100), 172 (96), 166 (11), 144 (7), 128 (18), 101 (15).

Anal. Calcd. For $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 60.11; H, 5.13; N 16.08.

Preparation of 5-(2-Furfurylidene)barbituric Acid (**8**).

Procedure B.

Mixture of barbituric acid (1.28 g; 0.01 mol) and 2-furaldehyde (0.96 g; 0.01 mol) in methanol (150 ml) was stirred at room temperature for five days. Methanol was evaporated at room temperature under reduced pressure. The solid residue was slurred in water (100 ml) stirred for two hours and solid residue separated by filtration. Crystalline product was washed with cold water (3x50 mL) and again slurred in ether. After filtration, the crystals were washed with ether (3x20 ml) and dried in the air resulting in a pure yellow crystalline product (1.67g; 81%). An analytical sample after drying in vacuum had mp 264 ºC with decomposition; lit. mp 260 ºC with decomposition [8]; IR (potassium bromide) 3520-3480, 1730, 1690, 1645, 1615-1590, 1560-1530 cm^{-1}; ^{1}H nmr: δ 11.35 (s, 1H, NH), 11.26 (s. 1H, NH), 8.45 (d, J = 0.012, 1H, aromatic-H), 8.24 (s, 1H, CH), 8.01 (s, 1H, aromatic-H), 6.90 (d, J = 0.008, aromatic-H); ^{13}C nmr: δ 159.8, 158.6, 147.7, 146.7, 133.4, 123.0, 111.8, 109.3.

Anal. Calcd. For $C_9H_6N_2O_4$: C, 52.44; H, 2.93; N, 13.59. Found: C, 52.36; H, 3.07; N 13.40

REFERENCES AND NOTES

[1a] For a historical account of barbituric acids see: M. K. Carter, *J. Chem. Ed.*, **28**, 524 (1951); Vogel's "A Text-Book of Practical Organic Chemistry", Third Edition, Wiley, New York, 1966; [b] J. T. Bojarski, J. L. Mokrosz, H. J. Barton, and M. H. Paluchowska, *Adv. Heterocycl. Chem*., **38**, 229 (1985); [c] W. J. Doran, *J. Med. Chem*., **4**, 1 (1959).

[2] K. S. Gulliya, U.S. Patent 5,869,494; *Chem Abstr*. (1999).

[3] K. G., U.S. Patent 5,674,870; *Chem Abstr.* (1997).

[4] K. Sakai and Y. Satoh, International Patent, WO9950252A3; *Chem Abstr* (2000).

[5] "The Merck Index", M. Windholz, Editor, 10th edition, Rahway 1983.

[6a] For a review see G. Jones, *Org. React.*, **15**, 204 (1967); [b] L. F. Tietze, U. Beifuss, in Comprehensive Organic Synthesis, B. M. Trost, I. Fleming, C. H. Heathcock, Eds. Pergoman press: Oxford, 1919; Vol **2**, Ch. 1.11, pp 341-394.

[7] A. Baeyer, *Liebigs Ann. Chem.*, **130**, 129 (1864).

[8] For uncatalyzed Knoevenagel condensation involving malononitrile see: F. Bigi, M. L. Conforti, R. Maggi, A. Piccinno, G. Sartori, *Green Chemistry*, **2** 101 (2000).

[9] V. D. Vvedenskii, *Khim. Geterotski. Soedin.*, **5**, 1092 (1969).

[10] D. Villemin and B. Labiad, *Synth. Commun.*, **20**, 3333 (1990).

[11] D. Villemin, *Chem. Commun.* 1092 (1983).

[12] B. P. Bandgar, S. M. Zirange, and P. P. Wadgaonkar, *Synth. Commun.*, **27**, 1153 (1997).

[13] S. Kim, P. Kwon, and T. Kwon, *Synth. Commun.*, **27**, 533 (1997).

[14] F. Jourdain and J. C. Pommelet, *Synth. Commun.*, **27**, 483 (1997).

[15] E. Obrador, M. Castro, J. Tamariz, G. Zepeda, R. Miranda, and F. Delgado, *Synth. Commun.*, **28**, 4649 (1998).

[16] G. Alcerreca, R. Sanabria, R. Miranda, G. Arroyo, J. Tamariz, and F. Delgado, *Synt. Commun.*, **30**, 1295 (2000).

[17] Determined by ^{1}H-nmr spectroscopy of the reaction mixture after evaporation of methanol at reduced pressure and room temperature. There is a clear difference in chemical shift for NH signals for the Knoevenagel condensation product (~11.25 and 11.35 ppm) and starting barbituric acid (~11.11 ppm). The ratio of the integrals for these signals is used to determine the percentage of the reaction conversion.

[18] For an aliphatic condensation reaction one can follow formation of the product by monitoring the intensity of the olefinic (CH=C) proton the NMR spectra.

[19] One can assume that preparation of these compounds can be facilitated by using different solvents as well as elevated temperatures. Formed products are exceptionally sensitive to both high temperature and acidic solvents. With high temperature they tend decompose (form many hard to identified products with polymeric tar) or with moderate heat and high acidic media, such as formic acid, one more step of cyclization occurs with the formation of 1,5-Dihydro-10-oxa-5-deazaflavins derivatives. These results will be published elsewhere.

[20] Aromatic conjugated products have deep red color which is due to both extended conjugation by the formation of a double bond between the barbituric and the aromatic moiety, as well as existence of the donor-acceptor interactions.