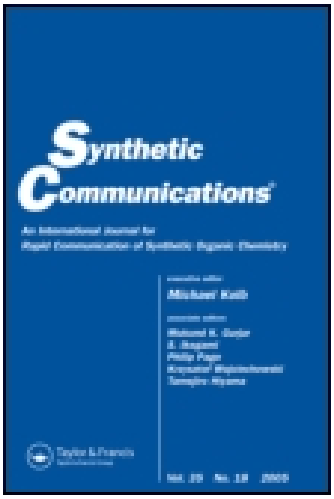

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HIGHLY EFFICIENT SYNTHESIS OF TRIOXOPYRIMIDINE-BASED CHALCONOIDS UNDER SOLVENT-FREE CONDITIONS

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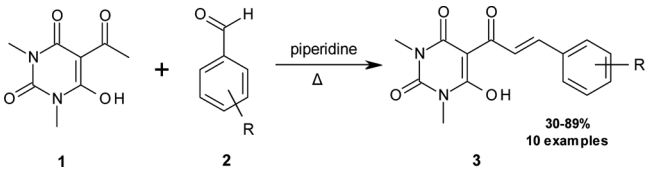
GRAPHICAL ABSTRACT



Abstract *Straightforward procedures for the fast and efficient synthesis of differently substituted barbituric acid–based chalconoids under solvent-free conditions were developed.*

Keywords Barbituric acid; chalconoids; screening; solvent-free reaction

INTRODUCTION

The 2,4,6-(1H,3H,5H)-pyrimidintrione fragment, or barbituric acid, is the structural basis of many biologically active compounds used in medicine nowadays. Besides common use as hypnotic, anaesthetic, and anticonvulsive,[1] barbituric acid derivatives possess anti-inflammatory,[2,3] antiviral,[4] immunosuppressive,[5] and cytostatic action.[6] Apart from pharmacology, barbituric acid derivatives are, for example, used in sensor systems, [7] as dyes,[8] and in pesticides.[9] Therefore, the development of new synthetic methods and the synthesis of libraries of new derivatives of oxopyrimidines is of importance.

The synthesis of trioxopyrimidine-based chalconoids **3** and their derivatives attracted significant attention in recent decades.[10–14] Reactions used are straightforward and employ variations of the aldol condensation,[14,15] Zn(L-proline)$_2$-catalyzed reactions in water,[11] solvent-free reactions of nitrogen-containing aldehydes,[12] microwave-assisted reactions,[13] and pyridine-catalyzed reactions in ethanol.[16]

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Our interest in synthesis of barbituric acid–based chalconoids started when investigating similar systems while working on the Knoevenagel condensation of imines under solvent-free conditions. By employing imines as reactants, it was not possible to obtain the desired results, and unexpectedly a highly efficient way of synthesizing chalconoids was discovered. This discovery was developed into the convenient solvent-free procedure presented here.

RESULTS AND DISCUSSION

The synthesis of 5-acetyl-1,3-dimethyl barbituric acid **1** was performed according to a well-established procedure.[17]

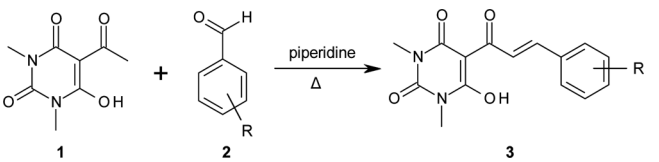
Chalconoids **3** were synthesized by reaction of 5-acetyl-1,3-dimethyl barbituric acid with a set of substituted benzaldehydes **2** under solvent-free conditions at elevated temperature, but unlike in the previously reported reaction where pyrazole carboxaldehyde was reacted,[12] a catalytic amounts of piperidine was added to the molten mixture of reactants, providing shorter reaction time. The role of the piperidine has not been investigated; however, one might be speculate that it may either function as base leading to increased nucleophilicity of the acetyl barbituric acid or it may increase the electrophilicity of the aldehyde by initial imine formation. In addition, products **3** with a melting point higher than the operating temperature of the reaction usually precipitated immediately from the mixture, providing a clear indication of product formation. Another advantage of the procedure was the simple workup, as the products were poorly soluble in boiling ethanol, thus facilitating the removal of by-products and unreacted starting materials.

Because yields varied for different substrates, it was decided to screen the reaction conditions to find out the importance of the individual variables affecting the outcome of the reaction.

SCREENING

A full factorial design[18,19] of eight experiments was chosen, with each variable kept at either high level (+) or low level (–), employing p-methoxy benzaldehyde as model substrate (Table 1).

Results from the analysis show that all variables should be kept at high level, and these conditions were applied to a set of differently substituted benzaldehydes, including electron-withdrawing and electron-donating substituents in the *para*- or *ortho*-positions (Table 2).



Scheme 1. Reaction of 5-acetyl-1,3-dimethyl barbituric acid with a range of substituted benzaldehydes. R = p-MeO, p-N(Me)$_2$, H, p-Cl, p-NO$_2$, o-MeO, o-Cl, o-CN, o-NO$_2$.

Table 1. Experimental design for screening of reaction conditions for the reaction between p-methoxy benzaldehyde and 5-acetyl-1,3-dimethyl barbituric acid

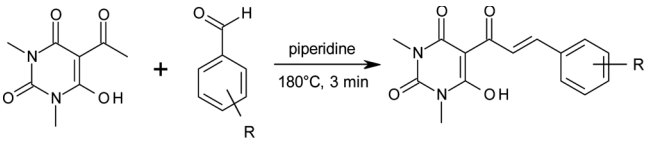
Variable	Level (–1)	Level (+1)	Experiment number	X1	X2	X3	Yield (%)
			1	–	–	–	31
X1 ratio[a]	1.2	2.0	2	+	–	–	50
			3	–	+	–	72
X2 time (min)[b]	1	3	4	+	+	–	75
			5	–	–	+	63
X3 temp. (°C)	120	180	6	+	–	+	85
			7	–	+	+	75
			8	+	+	+	88

[a]Ratio of aldehyde/barbituric acid.

[b]The reaction time was measured as the time from addition of piperidine to the time of removal of the reaction vessel from the oil bath.

As can be seen from the table, electron-donating substituents in the aromatic ring provide better yields under the chosen conditions than electron-withdrawing substituents. The fact that yields are higher for *para*-substituted compounds than for *ortho*-substituted compounds is probably due to steric factors. It was therefore of interest to investigate if better and/or general conditions could be found, and therefore screening of reaction variables was undertaken for o-nitro benzaldehyde. Initially it was believed that the reason for the poor yield was the reaction being slow and therefore the settings for the screening were set at 1 or 3 eq, 1 or 5 min, and 160 or 200°C. Results revealed that the ratio between aldehyde and acetyl barbituric acid should be set at the high level, as was the setting for time. On the other hand, the coefficient for temperature was negative, and consequently yields were higher at lower temperature. New experiments revealed that the great yields were obtained with 4 eq of benzaldehyde reacting for 7 min at 120°C, resulting in 52% of product.

Table 2. Yields from reaction of 5-acetyl-1,3-dimethyl barbituric acid with different aldehydes: R = p-MeO, p-$N(Me)_2$, H, p-Cl, p-NO_2, o-MeO, o-Cl, o-CN, o-NO_2



1 2 3

Compound	R	Isolated yield (%)
3a	H	76
3b	p-$N(Me)_2$	84
3c	p-OMe	89
3d	p-OH	76
3e	p-Cl	31
3f	p-NO_2	31
3g	o-OMe	65
3h	o-Cl	66
3i	o-CN	35
3j	o-NO_2	30

CONCLUSIONS

A new synthetic procedure for synthesis of α,β-unsaturated compounds was developed, revealing that to achieve optimum yields, reaction conditions have to be screened for each substrate.[20]

EXPERIMENTAL

(E)-5-(3-(4-Methoxyphenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (3c)

In a typical example, 5-acetyl-1,3-dimethybarbituric acid **1** (4 g, 20 mmol) was mixed with p-methoxybenzaldehyde (5.49 g, 40 mmol). The mixture was melted at 180 °C and 2–3 drops of piperidine were stirred into the mixture. Immediate change of the color of the reaction mixture was observed. After 2 min, the mixture solidified, providing yellow powder, which was allowed to cool to room temperature. The solid residue was boiled in ethanol (20 mL) for a few minutes and the precipitate was filtered off, rinsed with 20 ml of hot ethanol, and dried at room temperature, providing 5.6 g (89% yield) of **3c** as a bright yellow solid.

Mp 190–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 16.95 (d, J=1.4 Hz, 1 H), 8.46 (dd, J=15.7, 1.4 Hz, 1 H), 7.99 (d, J=15.8 Hz, 1 H), 7.65 (d, J=8.7 Hz, 2 H), 6.93 (d, J=8.8 Hz, 2 H), 3.86 (s, 3 H), 3.38 (6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.11, 170.02, 162.65, 161.68, 147.05, 131.41, 127.76, 117.99, 114.71, 93.97, 77.16, 55.64, 28.30, 28.09. IR (ν_{max}): 3108, 2955, 2845, 1711, 1654, 1622, 1598, 1506, 1481, 1418, 1257, 1168, 1017, 976, 824, 758 cm^{-1}. HRMS: calcd. for $C_{16}H_{15}O_5N_2$ [M$^-$] 315.0980, obs. 315.0986.

(E)-5-(3-(2-Nitrophenyl)acryloyl)-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (3j)

5-Acetyl-1,3-dimethybarbituric acid **1** (0.144 g, 0.73 mmol) was mixed with o-nitrobenzaldehyde (0.437 g, 2.9 mmol). The mixture was melted at 120 °C and 1 drop of piperidine was stirred into the mixture. After 7 min, heating was discontinued, and the mixture was allowed to cool to room temperature. The residue was boiled in ethanol (2 mL) for a few minutes, and the precipitate was filtered off, rinsed with 2 ml of hot ethanol, and dried at room temperature, providing 0.13 g (52%) of **3j** as a pale yellow solid.

Mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 17.08 (s, 1 H), 8.50 (d, J=15.7 Hz, 1 H), 8.40 (d, J=15.7 Hz, 1 H), 8.05 (dd, J=8.1, 1.2 Hz, 1 H), 7.86 (dd, J=7.8, 1.1 Hz, 1 H), 7.68 (m, J=7.8, 1.2, 0.7 Hz, 1 H), 7.57 (td, J=8.1, 1.4 Hz, 1 H), 3.38 (m, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 183.01, 169.96, 161.42, 150.41, 148.86, 141.00, 133.69, 130.97, 130.87, 129.73, 125.38, 125.14, 95.29, 28.38, 28.21. IR (ν_{max}): 3105, 3079, 2963, 1721, 1672, 1623, 1571, 1514, 1473, 1421, 1353, 1339, 1298, 1212, 1016, 974, 925, 791, 752, 745 cm^{-1}.

HRMS: calcd. for $C_{15}H_{13}O_6N_3Na$ [M+Na]$^+$ 354.0697, obs. 354.0698.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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