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An efficient acylation/base-catalyzed cyclization of thioureas affords *N*,*N*′-disubstituted thiobarbituric acids

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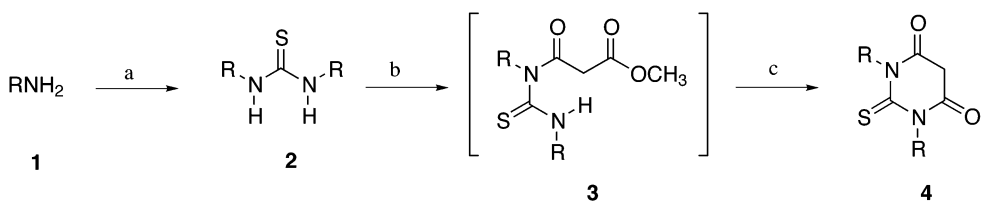
Abstract—Acylation of 1,3-disubstituted thioureas with methyl malonyl chloride followed by base-catalyzed cyclization leads to the preparation of 1,3-disubstituted-2-thiobarbituric acids in high yield. © 2001 Published by Elsevier Science Ltd.

Certain substituted 2-thiobarbituric acids have long been used as intravenous anesthetics[1] and as intermediates in the preparation of dyes.[10a] More recently there has been interest in 2-thiobarbituric acids as anticonvulsants,[2] immunotropic and anti-inflammatory compounds,[3] anti-neoplastic agents,[4] and as platforms in the synthesis of other biologically active compounds.[5] While deceptively simple in structure, 1,3-disubstituted-2-thiobarbituric acids have been prepared in only three ways.[6] Simple 1,3-dialkyl substituted-2-thiobarbituric acids are prepared in high yield by the base-catalyzed condensation of dialkyl malonate esters with alkyl substituted thioureas.[7] However, this protocol has not been reported for the preparation of 1,3-diaryl and 1,3-diarylalkyl substituted thiobarbituric acids.[8] Rather, they are prepared by the condensation of substituted thioureas with malonyl dichloride,[2,3,9] or with malonic acid and acetyl chloride.[2b,10] The former protocol, while reported to generate 1,3-diaryl-2-thiobarbituric acids in 50% yield, has not been reported for the preparation of 1,3-diarylalkyl-2-thiobarbituric acids. The latter protocol has been used to prepare 1,3-diarylalkyl-2-thiobarbituric acids in yields of <10%.[10b] We report herein our work on the development of an efficient synthesis of 1,3-diarylalkyl substituted 2-thiobarbituric acids by the acylation and base-catalyzed cyclization of substituted thioureas and the extension of this methodology to the preparation of 1,3-diaryl substituted 2-thiobarbituric acids (Scheme 1).

Substituted arylalkyl amines (**1**) were reacted with 1,1′-thiocarbonyldiimidazole to afford substituted thioureas (**2**) in 95% yield. These thioureas were reacted with malonyl dichloride, however the excessive reactivity of this reagent led to poor yields of the 2-thiobarbituric acids (**4**). The less reactive methyl malonyl chloride[11] was substituted for malonyl dichloride and when combined with **2** in refluxing 1,2-dichloroethane afforded **4** in 16–60% yields. The HCl formed from the condensation of methyl malonyl chloride and **2** was thought to catalyze the cyclization to **4**.



Scheme 1. (a) 1,1′-Thiocarbonyldiimidazole/ACN 0°C; (b) methyl malonyl chloride/1,2-dichloroethane/reflux 15 min; (c) 1N NaOH/EtOAc/rt. R = $Ar(CH_2)_n$–; n = 1,2.

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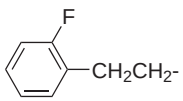
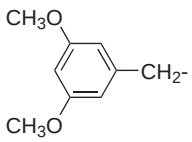
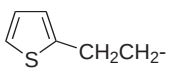
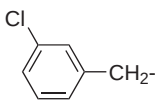
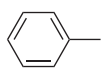
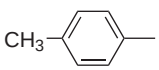
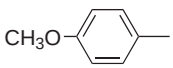
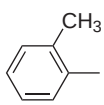
The reaction between **2** and methyl malonyl chloride proved to be problematic. The yields were low and often not reproducible. The reaction times were excessive, in one case requiring 72 hours at reflux for completion. Moreover, the impurities formed during the cyclization made isolation and purification of the products difficult. Therefore, to better understand the mechanism, the conversion was monitored by HPLC and NMR spectroscopy. Both techniques showed the formation of an intermediate, that on the basis of NMR spectroscopy, was identified as an *N*-acylthiourea (**3**). This intermediate was formed nearly quantitatively within 15 minutes at 83°C. The only byproduct observed was the diacylthiourea, which was present in $\leq 2\%$. Prolonged heating of the reaction mixture at 83°C in the presence of HCl led to the formation of **4** and impurities as well as a small amount of **2**. However, we found that **3** was stable enough to be isolated and slowly cyclized to **4** over the course of several days when stored at ambient temperature.

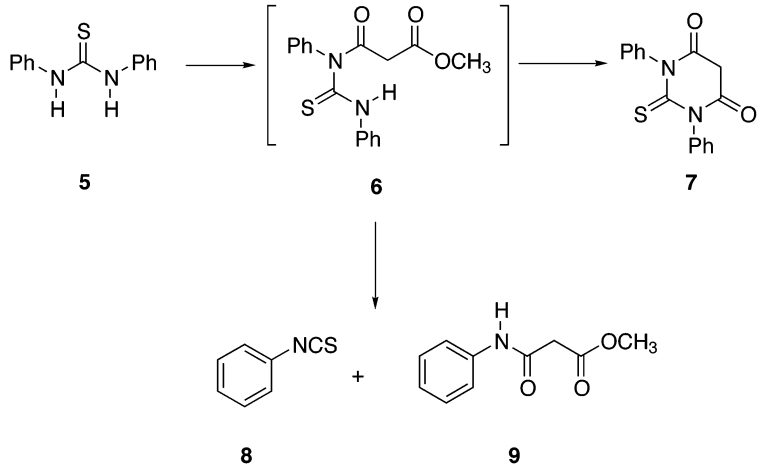
We next turned our attention to the cyclization of **3** under basic conditions. The base-catalyzed condensation of thiourea and diethylmalonate is well known in the literature[7a,b] and leads to quantitative yields of 2-thiobarbituric acid. We felt that the cyclization of **3** under basic conditions would likewise lead to high yields of **4**. Thus, treatment of **3** with a slight excess of aqueous NaOH at 23°C led quantitatively to **4**. The yields after recrystallization were 87–90% (Table 1).[12] The protocol was effective for the preparation of both benzyl and 2-phenethyl substituted thioureas. We found the yield of the reaction was unaffected by the presence of either electron withdrawing or electron donating substituents on the aromatic groups. The protocol can be conveniently run on 100 g scale without any loss in yield.

We then examined the preparation of 1,3-diaryl-2-thiobarbituric acids with the newly developed protocol.

Table 1. Preparation of 1,3-disubstituted-2-thiobarbituric acids **4** from *N*,*N*′-disubstituted thioureas **2**

Entry	R	Condition[a]	Yield (%)
1		A	87
2		A	87
3		A	88
4		A	90
5		B	85
6		B	84
7		B	90
8		B	43

[a] A: methyl malonyl chloride, 1,2-dichloroethane, reflux, then NaOH, EtOAc; B: 2 equiv of methyl malonyl chloride, CH_2Cl_2, rt, then conc. under vacuum, rt



Scheme 2.

Treatment of thiocarbanilide (**5**) with methyl malonyl chloride in refluxing 1,2-dichloroethane led primarily to the formation of phenylisothiocyanate (**8**) and the mixed ester amide (**9**) (Scheme 2). The identity of **8** and **9** were established by GC/MS. The identity of **9** was also confirmed by comparison to an authentic sample of the mixed amide ester prepared by the reaction of aniline with methyl malonyl chloride. Compounds **8** and **9** were thought to be formed through thermal rearrangement of the intermediate *N*-acylthiourea (**6**). We overcame the thermal instability of **6** by performing the reaction at 23–25°C with 2 equiv. of methyl malonyl chloride in methylene chloride. A slow stream of nitrogen was passed over the reaction mixture to remove HCl formed during the reaction. This modified protocol provided high yields of **6**. However, treatment of **6** with aqueous NaOH at 23–25°C again led primarily to the formation of **8** and **9**. Noting earlier that **3** cyclized spontaneously to **4** when isolated as an oil, **6** was similarly concentrated to an oil. After concentration to an oil, **6** cyclized to **7** over the course of several days at 23–25°C. The crude product (**7**) was purified by reslurrying in hot methyl *t*-butyl ether. The modified protocol afforded excellent yields of 1,3-diaryl substituted-2-thiobarbituric acids (Table 1, entries 5–7).[13] However, the sterically congested 1,3-di-*o*-tolyl thiourea produced only a moderate yield of product (entry 8).

In summary, an efficient and high-yielding synthesis of 1,3-diarylalkyl and 1,3-diaryl substituted 2-thiobarbituric acids from 1,3-disubstituted thioureas and methyl malonyl chloride has been realized.

Acknowledgements

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11. Methyl malonyl chloride (methyl 3-chloro-3-oxopropionate) is available from Aldrich.
12. Representative procedure for the preparation of 1,3-diarylalkyl-2-thiobarbitutric acids: Methyl malonyl chloride (25.6 mL, 0.24 mol) was added dropwise to a suspension of *N*,*N*′-di-(3-chlorobenzyl) thiourea (65 g, 0.19 mol) in dry 1,2-dichloroethane (100 mL). The reaction mixture was heated at reflux for 15 minutes and then cooled to 25°C. The solvent was evaporated and replaced with ethyl acetate (650 mL). 1N NaOH (250 mL) was added and the two-phase mixture was stirred for 2 h at 23°C. The solvent was then evaporated from the organic layer and the residue was purified by recrystallization from ethanol (400 mL) to give 73.1 g (90%) of 1,3-di-(3-chlorobenzyl)-2-thiobarbituric acid as a yellow solid.
13. Representative procedure for the preparation of 1,3-diaryl-2-thiobarbituric acids: Methyl malonyl chloride (2.06 mL, 19.2 mmol) was added dropwise to a suspension of *N*,*N*′-di-(4-methoxyphenyl) thiourea (2.52 g, 8.76 mmol) and methylene chloride (100 mL). The solids dissolved within 15 minutes. A slow nitrogen stream was passed over the reaction, while stirring at 20–23°C. After stirring for 24 h most of the solvent had evaporated. HPLC of the residue indicated complete conversion of starting material to the *N*-acylthiourea intermediate. The remaining solvent was evaporated and the residue was placed under vacuum. The progress of the cyclization was monitored by HPLC and after 48 h, the conversion to thiobarbituric acid was complete. The resulting yellow solid was broken up with a spatula and purified by refluxing in 25 mL of methyl *t*-butyl ether to give 2.8 g (90%) of 1,3-di-(4-methoxyphenyl)-2-thiobarbituric acid.