

Self-condensation of Arylthioacetamides: Novel Syntheses of 3-Aminothioacrylamides, 2,4-Diaminothiophenes and Four-membered-ring Vinamidinium Salts

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Self-condensation of arylthioacetmorpholides **1** in the presence of *N,N*-disubstituted amides **2** and POCl₃ gave 2-aryl-3-benzyl-3-morpholiniothioacrylamides **4**, which were converted to four-membered-ring vinamidinium salts **5** or 2,4-dimorpholino-3,5-diarylthiophenes **6** by novel synthesis of the thiophene ring.

3-Aminothioacrylamides **3** are widely used as starting materials in syntheses of heterocyclic and open-chain compounds.¹ They can be prepared in different principal ways.² The iminoformylation of arylthioacetamides **1** with amides **2** and POCl₃ is particularly useful in the synthesis of *N,N,N',N'*-tetrasubstituted 2-arylthioacrylamides **3** (R¹ = H).³ We report now on attempts to extend this synthesis to 3-substituted 3-aminothioacrylamides **3** (R¹ ≠ H) by applying amides **2** different from formamides.

Reaction of arylthioacetamides **1** with *N,N*-dimethylacetamide **2** (R¹ = Me) and POCl₃ gives yellow oils consisting of the expected **3** but containing 3-benzyl-3-morpholiniothioacrylmorpholides **4** as byproducts. The latter compounds become major products if *N,N*-disubstituted benzamides **2** (R¹ = Ph), *N*-methylpyrrolidone **2** [R¹R² = (CH₂)₃, R³ = Me] or, most effectively, phenylacetmorpholide **2** (R¹ = CH₂Ph, NR²R³ = morpholino) are employed in reactions with **1** and POCl₃.[†] In one case (R¹ = Ph, R² = R³ = Et) the corresponding thioamide R¹CSNR²R³ was found as further byproduct. Re-investigations of the known iminoformylation³ of arylthioacetamides **1** with DMF **2** (R¹ = H, R² = R³ = Me)–POCl₃ revealed that traces of **4** are also formed in these cases.

Obviously the 3-benzyl-3-morpholiniothioacrylmorpholides **4** are formed by self-condensation of the arylthioacetamides **1**. As far as we know this is the first case known for an ester condensation type reaction in the thioamide series. Unlike the classical ester condensation which requires basic conditions,

the transformation of thioamides **1** into thioacrylamides **4** occurs under acidic conditions. In this respect it resembles the known⁴ self-condensation of substituted acetamide chlorides and eventually runs *via* intermediates **7** (X = Cl or SCR¹=N⁺R²R³).

First investigations of the reaction behaviour of the new 3-benzyl-3-morpholiniothioacrylamides **4** revealed interesting phenomena, which were not found in compounds **3** lacking the 3-benzyl substituent (R¹ ≠ PhCH₂). Methylation of **4** with methyl iodide and subsequent treatment with triethylamine gives rise to four-membered-ring vinamidinium salts **5**.[‡] Probably the expected *S*-methylation product is deprotonated (formation of **8**) or eliminates methylthiol (formation of a corresponding keteniminium salts) and is further cyclized possibly by intramolecular 2 + 2 cycloaddition. Similar cyclic vinamidinium salts **5** are known to be formed by intermolecular 2 + 2 cycloaddition of keteniminium salts and ynamines.^{5,6}

A further unexpected result was found when 3-benzyl-3-morpholiniothioacrylmorpholides **4** were treated with methylglycinate in dioxane solution. Instead of the anticipated substitution products (2-aryl-3-benzyl-3-methoxycarbonylmethylaminiothioacrylmorpholides) the 2,4-dimorpholino-3,5-diphenylthiophenes **6** were obtained in high yield without incorporating the glycinate. 2,4-Diaminothiophenes are hardly found in the literature.^{7,8} It could be proved that this novel synthesis of the thiophene ring (formation of **6**) is caused by oxidation. The scope of this interesting ring closure, which is somehow related to oxidative cyclizations of mercapto-butadiene systems,⁹ is currently being investigated.

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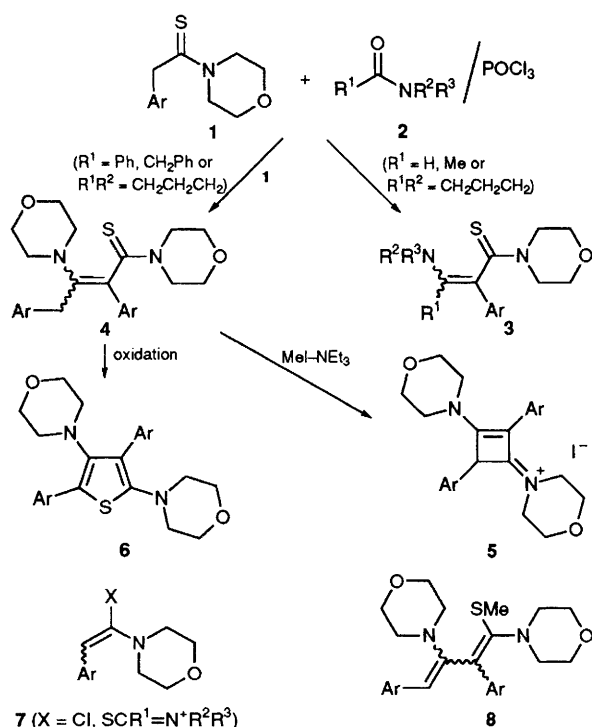
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Footnotes

[†] Typical procedure (**4a**): POCl₃ (2.5 g, 14.6 mmol) was added drop wise to a solution of phenylacetmorpholide (**3** g, 14.6 mmol) in CCl₄ (30 ml) while stirring and cooling with ice/NaCl. Phenylthioacetmorpholide **1** (Ar = Ph) (3.2 g, 14.4 mmol) was then added at room temperature. After 30 min of reflux (continued stirring) the CCl₄ phase was separated. The remaining red oil was dissolved in CHCl₃ (about 150 ml) and washed with water several times. After drying over Na₂SO₄ and evaporation of the solvent the remainder was crystallized from MeCN.

Table 1 3-Aminothioacrylamides **3** and **4**, vinamidinium iodide **5a** and 2,4-dimorpholino-3,5-diphenylthiophene **6a**

Product	Ar	R ¹	R ²	R ³	Yield (%)	mp/°C
3a	4-ClC ₆ H ₄	Me	Me	Me	48	Oil
3b	Ph	(CH ₂) ₃	—	Me	16	98–100
4a	Ph	—	—	—	92	208–210
5a	Ph	—	—	—	66	155–157
6a	Ph	—	—	—	87	175–177



Scheme 1 Synthesis of 2-aryl-3-benzyl-3-morpholiniothioacrylmorpholides and their transformation to four-membered-ring vinamidinium salts and 2,4-dimorpholinothiophenes

‡ A mixture of 3-morpholinothioacrylamide **4a** (Ar = Ph) (1.02 g, 2.5 mmol), MeI (0.43 g, 3 mmol) and MeOH (50 ml) was stirred at room temperature until all the starting material disappeared (about 30 min, deep yellow solution). After addition of NEt₃ (0.3 g, 3 mmol) the solution was refluxed for 30 min (formation of methylthiole). The almost colourless solution was combined with water (ca. 100 ml) and extracted with CHCl₃. After drying and evaporation of the solvent the remaining solid was dissolved in a small amount of MeOH and reprecipitated by dilution with Et₂O.

§ All compounds exhibited satisfactory analytical data. *Spectral data:* **4a**, ¹³C NMR (CDCl₃, 75 MHz) (major isomer), δ 38.97, 49.36, 50.18, 51.53, 65.98, 66.52, 66.85, 121.92, 126.92, 128.32, 128.43, 128.83, 129.14, 129.34, 138.47, 139.03, 146.02, 201.53; MS (70 eV), *m/z* 408 (M⁺, 28), 375 (M – SH, 63), 91 (100). **5a**; ¹³C NMR (CDCl₃, 75 MHz) δ 48.37, 49.06, 65.47, 66.27, 109.94, 132.43, 130.00, 130.42, 129.67, 162.96; ¹H NMR (CDCl₃, 250 MHz) δ 3.1–3.3 (m, 4H), 3.36–3.50 (m, 4H), 3.55–3.68 (m, 4H), 3.75–3.85 (m, 2H), 3.93–4.03 (m, 2H), 6.20 (s, 1H), 7.43–7.70 (aromatic H, 10H). **6a**; ¹³C NMR (CDCl₃, 75 MHz) δ 51.59, 52.66, 66.68, 67.13, 120.40, 126.62, 126.75, 127.23, 127.29, 128.02, 129.99, 130.17, 134.87, 135.90, 143.94, 151.92; ¹H NMR

(CDCl₃, 300 MHz), δ 2.71 (m, 4H), 2.80 (m, 4H), 3.40 (m, 4H), 3.58 (m, 4H), 7.23–7.57 (aromatic H, 10H);

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