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

Andreas Rolfs and Jürgen Liebscher*

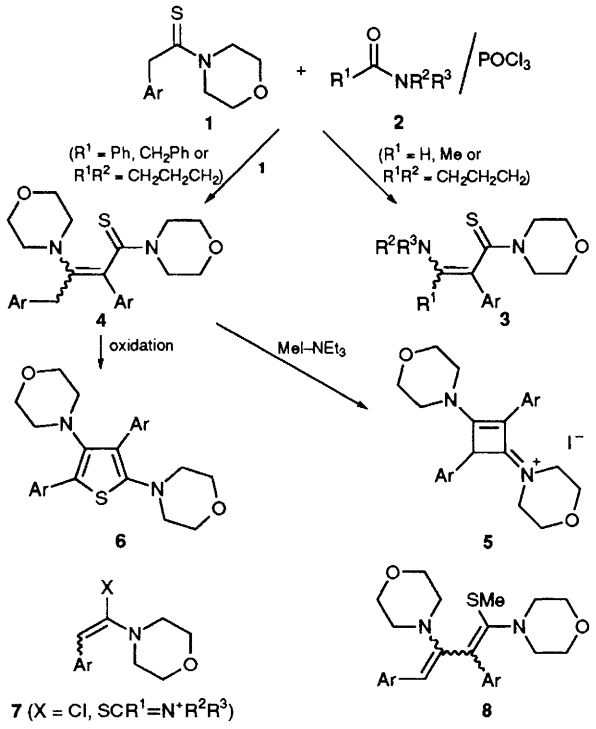
Fachbereich Chemie, Humboldt-Universität Berlin, Hessische Str. 1-2, D-10115 Berlin, Germany

Self-condensation of arylthioacetmorpholides **1** in the presence of *N,N*-disubstituted amides **2** and $POCl_3$ gave 2-aryl-3-benzyl-3-morpholinothioacrylamides **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 $POCl_3$ is particularly useful in the synthesis of *N,N,N',N'*-tetrasubstituted 2-arylthioacrylamides **3** (R^1 = H).[3] We report now on attempts to extend this synthesis to 3-substituted 3-aminothioacrylamides **3** ($R^1 \neq$ H) by applying amides **2** different from formamides.

Reaction of arylthioacetamides **1** with *N,N*-dimethylacetamide **2** (R^1 = Me) and $POCl_3$ gives yellow oils consisting of the expected **3** but containing 3-benzyl-3-morpholinothioacrylmorpholides **4** as byproducts. The latter compounds become major products if *N,N*-disubstituted benzamides **2** (R^1 = Ph), *N*-methylpyrrolidone **2** [$R^1R^2 = (CH_2)_3$, R^3 = Me] or, most effectively, phenylacetmorpholide **2** ($R^1 = CH_2Ph$, NR^2R^3 = morpholino) are employed in reactions with **1** and $POCl_3$.† In one case (R^1 = Ph, $R^2 = R^3$ = Et) the corresponding thioamide $R^1CSNR^2R^3$ was found as further byproduct. Re-investigations of the known iminoformylation[3] of arylthioacetamides **1** with DMF **2** (R^1 = H, $R^2 = R^3$ = Me)–$POCl_3$ revealed that traces of **4** are also formed in these cases.

Obviously the 3-benzyl-3-morpholinothioacrylmorpholides **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 known[4] self-condensation of substituted acetamide chlorides and eventually runs *via* intermediates **7** (X = Cl or $SCR^1{=}N^+R^2R^3$).



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

First investigations of the reaction behaviour of the new 3-benzyl-3-morpholinothioacrylamides **4** revealed interesting phenomena, which were not found in compounds **3** lacking the 3-benzyl substituent ($R^1 \neq PhCH_2$). 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-morpholinothioacrylmorpholides **4** were treated with methylglycinate in dioxane solution. Instead of the anticipated substitution products (2-aryl-3-benzyl-3-methoxycarbonylmethylaminothioacrylmorpholides) 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 mercaptobutadiene systems,[9] is currently being investigated.

We thank the Arzneimittelwerk Dresden GmbH and the Fonds der Chemischen Industrie for financial support.

Received, 4th March 1994; Com. 4/01321B

Footnotes

† *Typical procedure* (**4a**): $POCl_3$ (2.5 g, 14.6 mmol) was added drop wise to a solution of phenylacetmorpholide (3 g, 14.6 mmol) in CCl_4 (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 CCl_4 phase was separated. The remaining red oil was dissolved in $CHCl_3$ (about 150 ml) and washed with water several times. After drying over Na_2SO_4 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_6H_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

‡ 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 NEt_3 (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 $CHCl_3$. After drying and evaporation of the solvent the remaining solid was dissolved in a small amount of MeOH and reprecipitated by dilution with Et_2O.

§ All compounds exhibited satisfactory analytical data. *Spectral data*: **4a**, ^{13}C NMR ($CDCl_3$, 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**; ^{13}C NMR ($CDCl_3$, 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 ($CDCl_3$, 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**; ^{13}C NMR ($CDCl_3$, 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 ($CDCl_3$, 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);

References

1 J. Liebscher, Berhanu Abegaz and A. Knoll, *Phosphorus Sulfur*, 1988, **35**, 5.
2 J. Liebscher, A. Knoll and Berhanu Abegaz, *Z. Chem.*, 1987, **27**, 8.
3 J. Liebscher and Berhanu Abegaz, *Synthesis*, 1982, 769.
4 H. Eilingsfeld, M. Seefelder and H. Weidinger, *Angew. Chem.*, 1960, **72**, 836.
5 H. G. Viehe, R. Buijle, R. Fuks, R. Merenyi and J. M. F. Oth, *Angew. Chem.*, 1967, **79**, 53; *Angew. Chem., Int. Ed. Engl.* 1967, **6**, 77.
6 J. Ficini and C. Barbara, *Tetrahedron Lett.*, 1966, **52**, 6425.
7 R. K. Norris, in *The Chemistry of Hetercyclic Compounds*, ed. S. Gronowitz, 1986, vol. 44/II, p. 658.
8 J. P. Chupp, *J. Heterocycl. Chem.*, 1970, **7**, 285.
9 E. Campaigne, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, 1984, vol. 4/III, p. 865.