# Synthesis of arylmethylenecyanothioacetamides in a Michael reaction

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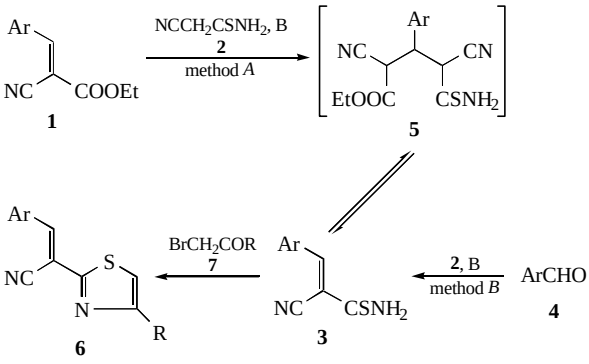
Interaction of arylmethylenecyanoacetic esters and cyanothioacetamide in the presence of *N*-methylmorpholine leads to formation of arylmethylenecyanothioacetamides, which have been used in the synthesis of substituted thiazoles.

It is known that arylmethylenecyanothioacetamides may be obtained by the condensation of an aromatic aldehyde and cyanothioacetamide in the presence of amines.[1–3] We found that the interaction of arylmethylenecyanoacetic esters **1** and cyanothioacetamide **2** in ethanol at room temperature in the presence of an equimolar quantity of *N*-methylmorpholine leads to formation of arylmethylenecyanothioacetamides **3** (method *A*),[†] also obtained by the condensation of aromatic aldehydes **4** with cyanothioacetamide **2** (method *B*). This type of transformation involving exchange of methylene components is already known,[4] but exchange of cyanoacetic ester for cyanothioacetamide is novel. It is known that the reaction of arylmethylenecyanoacetic esters (Ar = 4-$ClC_6H_4$, 4-$BrC_6H_4$, Ph) with cyanothioacetamide leads to formation of 4-aryl-6-oxy-3,5-dicyanopyridin-2(1*H*)-thiones.[5,6] The above-mentioned exchange of methylene components in a Michael reaction may be accounted for by the presence of electron-donating groups in the aromatic ring, which promotes deactivation of the double bond in the compounds **1**. This leads to disintegration of the hypothetical adduct **5** by means of formation of a new C=C bond with elimination of the less nucleophilic anion. In addition, arylmethylenecyanothioacetamides **3** are less soluble in ethanol than compounds **1**. This leads, according Le Chatelier's principle, to displacement of the reaction equilibrium towards formation of products **3**.

The structure of the compounds **3** was confirmed by $^1$H NMR spectral data and by involvement of the compounds **3** in a Hantzsch-type condensation, from which substituted thiazoles **6** were obtained.[‡]




B = *N*-methylmorpholine

| **1**,**3**,**4** | Ar |
|---|---|
| **a** | 2,4-$(EtO)_2C_6H_3$ |
| **b** | 3,4-$(MeO)_2C_6H_3$ |
| **c** | 4-$BuOC_6H_4$ |
| **d** | 4-$Me_2NC_6H_4$ |

| **7** | R |
|---|---|
| **a** | 4-$BuC_6H_4$ |
| **b** | 2-thienyl |
| **c** | 3-cumarinyl |
| **d** | 4-$PhC_6H_4$ |
| **e** | 4-$BrC_6H_4$ |
| **f** | Ph |
| **g** | 4-$MeC_6H_4$ |

| **6** | Ar | R |
|---|---|---|
| **a** | 2,4-$(EtO)_2C_6H_3$ | 4-$ClC_6H_4$ |
| **b** | 2,4-$(EtO)_2C_6H_3$ | 4-$MeC_6H_4$ |
| **c** | 2,4-$(EtO)_2C_6H_3$ | 4-$BuC_6H_4$ |
| **d** | 2,4-$(EtO)_2C_6H_3$ | Ph |
| **e** | 2,4-$(EtO)_2C_6H_3$ | 3-cumarinyl |
| **f** | 2,4-$(EtO)_2C_6H_3$ | 4-$PhC_6H_4$ |
| **g** | 2,4-$(EtO)_2C_6H_3$ | 3,4-$Cl_2C_6H_3$ |
| **h** | 2,4-$(EtO)_2C_6H_3$ | 4-$BrC_6H_4$ |
| **i** | 4-$Me_2NC_6H_4$ | 4-$BuC_6H_4$ |
| **j** | 4-$BuOC_6H_4$ | 4-$BrC_6H_4$ |
| **k** | 3,4-$(MeO)_2C_6H_3$ | 4-$PhC_6H_4$ |
| **l** | 3,4-$(MeO)_2C_6H_3$ | 2-thienyl |
| **m** | 3,4-$(MeO)_2C_6H_3$ | 4-$BuC_6H_4$ |

**Scheme 1**

## References

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[†] *Arylmethylenecyanothioacetamides* **3a**–**d**. Method *A*. A mixture of 10 mmol of compound **1**, 10 mmol of cyanothioacetamide **2** and 10 mmol of *N*-methylmorpholine in 15 ml of ethanol was stirred at 20 °C during 40 min. The precipitate was filtered and washed with ethanol and hexane. Compounds **3a**–**d** were obtained and recrystallized from ethanol (Table 1).

Method *B*. To a mixture of 10 mmol of aldehyde **4** and 10 mmol of cyanothioacetamide **2** in 15 ml of ethanol was added one drop of *N*-methylmorpholine, and the resulting mixture was stirred at 20 °C during 30 min. The precipitate was filtered and washed with ethanol and hexane (Table 1).

Compound **3d** is known.[1] Its yield by method *A* was 84%, and 86% by method *B*, mp 232–233 °C.

[‡] 3-*Aryl*-2-(4-R-*thiazol*-2-*yl*)*acrylonitriles* **6a**–**m**. To a solution of 10 mmol of the compound **3** in 10 ml of dimethylformamide at 20 °C was added 10 mmol of α-bromoketone **7** and the mixture was stirred during 3 h. The resulting precipitate was filtered and washed with water, ethanol and hexane (Table 1).

**Table 1** Characteristics of compounds **3a**–**c** and **6a**–**m**.

| Compound | Yield (%) method *A*/*B* | Mp/°C | $^1$H NMR spectra ($\delta$, [$^2H_6$]DMSO) |
|---|---|---|---|
| **3a** | 76/82 | 178–180 | 9.94 and 9.37 (s, 2H, $NH_2$), 8.43 (s, 1H, CH=), 8.10 and 6.71 (d, 2H, $C_6H_3$), 6.67 (s, 1H, $C_6H_3$), 4.16 (q, 4H, $2CH_2$), 1.38 (t, 3H, $CH_3$), 1.36 (t, 3H, $CH_3$) |
| **3b** | 82/83 | 198–200 | 9.95 and 9.43 (s, 2H, $NH_2$), 8.08 (s, 1H, CH=), 7.69 (s, 1H, $C_6H_3$), 7.58 and 7.15 (d, 2H, $C_6H_3$), 3.88 and 3.83 (s, 6H, $2CH_3$) |
| **3c** | 85/94 | 131–132 | 9.98 and 9.46 (s, 2H, $NH_2$), 8.07 (s, 1H, CH=), 7.97 and 7.13 (d, 4H, $C_6H_4$), 4.09 (t, 2H, $OCH_2$), 1.15–1.85 [m, 4H, $(CH_2)_2$], 0.94 (t, 3H, $CH_3$) |
| **6a** | 77 | 143–145 | 8.40 (s, 1H, CH=), 8.22 (s, 1H, thiazolyl), 8.15 and 6.75 (d, 2H, $C_6H_3$), 6.66 (s, 1H, $C_6H_3$), 8.02 and 7.53 (d, 4H, $C_6H_4$), 4.15 (m, 4H, $2CH_2$), 1.41 and 1.36 (t, 6H, $2CH_3$) |
| **6b** | 81 | 135–137 | 8.43 (s, 1H, CH=), 8.20 (s, 1H, thiazolyl), 8.07 and 6.71 (d, 2H, $C_6H_3$), 6.67 (s, 1H, $C_6H_3$), 7.89 and 7.27 (d, 4H, $C_6H_4$), 4.18 (m, 4H, $2CH_2$), 2.35 (s, 3H, $CH_3$), 1.41 and 1.36 (t, 6H, $2CH_3$) |
| **6c** | 72 | 94–95 | 8.40 (s, 1H, CH=), 8.13 (s, 1H, thiazolyl), 8.06 and 6.72 (d, 2H, $C_6H_3$), 6.63 (s, 1H, $C_6H_3$), 7.88 and 7.26 (d, 4H, $C_6H_4$), 2.59 (t, 2H, $OCH_2$), 1.42 and 1.37 (t, 6H, $2CH_3$), 1.60 [m, 4H, $(CH_2)_2$], 0.89 (t, 3H, $CH_3$) |
| **6d** | 84 | 134–135 | 8.38 (s, 1H, CH=), 8.15 (s, 1H, thiazolyl), 8.02 and 6.71 (d, 2H, $C_6H_3$), 6.61 (s, 1H, $C_6H_3$), 7.44 (m, 5H, Ph), 4.10 (m, 4H, $2CH_2$), 1.38 and 1.32 (t, 6H, $2CH_3$) |
| **6e** | 85 | 194–196 | 8.68 (s, 1H, cumarinyl), 8.38 (s, 1H, CH=), 8.18 (s, 1H, thiazolyl), 8.02 and 6.70 (d, 2H, $C_6H_3$), 6.61 (s, 1H, $C_6H_3$), 7.37–7.79 (m, 4H, $H_{arom}$), 4.14 (m, 4H, $2CH_2$), 1.44 and 1.37 (t, 6H, $2CH_3$) |
| **6f** | 90 | 174–176 | 8.45 (s, 1H, CH=), 8.19 (s, 1H, thiazolyl), 8.11 and 6.85 (d, 2H, $C_6H_3$), 6.67 (s, 1H, $C_6H_3$), 7.46–7.75 (m, 9H, $H_{arom}$), 4.16 (m, 4H, $2CH_2$), 1.42 and 1.37 (t, 6H, $2CH_3$) |
| **6g** | 77 | 129–131 | 8.30 (s, 1H, CH=), 8.15 (s, 1H, thiazolyl), 8.11 and 6.67 (d, 2H, $C_6H_3$), 6.56 (s, 1H, $C_6H_3$), 7.64–7.89 (m, 3H, $H_{arom}$), 4.10 (m, 4H, $2CH_2$), 1.42 and 1.35 (t, 6H, $2CH_3$) |
| **6h** | 91 | 145–146 | 8.40 (s, 1H, CH=), 8.24 (s, 1H, thiazolyl), 8.15 and 6.74 (d, 2H, $C_6H_3$), 6.66 (s, 1H, $C_6H_3$), 7.94 and 7.66 (d, 4H, $C_6H_4$), 4.16 (m, 4H, $2CH_2$), 1.41 and 1.36 (t, 6H, $2CH_3$) |
| **6i** | 74 | 128–130 | 8.10 (s, 1H, CH=), 7.91 (s, 1H, thiazolyl), 7.85 (m, 4H, $H_{arom}$), 7.26 and 6.82 (d, 4H, $C_6H_4$), 3.07 (s, 6H, $2CH_3$), 2.62 (t, 2H, $CH_2$), 1.15–1.70 [m, 4H, $(CH_2)_2$], 0.92 (t, 3H, $CH_3$) |
| **6j** | 75 | 109–111 | 8.27 (s, 1H, CH=), 8.21 (s, 1H, thiazolyl), 8.00 and 7.09 (d, 4H, $C_6H_4$), 7.95 and 7.64 (d, 4H, $C_6H_4$), 4.05 (t, 2H, $OCH_2$), 1.25–1.84 [m, 4H, $(CH_2)_2$], 0.92 (t, 3H, $CH_3$) |
| **6k** | 80 | 187–189 | 8.30 (s, 1H, CH=), 8.15 (s, 1H, thiazolyl), 8.10 and 7.70 (d, 4H, $C_6H_4$), 7.80 (s, 1H, $C_6H_3$), 7.45 and 7.15 (d, 2H, $C_6H_3$), 3.89 and 3.87 (s, 6H, $2CH_3$) |
| **6l** | 71 | 159–161 | 8.19 (s, 1H, CH=), 8.06 (s, 1H, thiazolyl), 7.74 (m, 4H, $H_{arom}$), 7.15 (m, 2H, thienyl), 3.87 and 3.84 (s, 6H, $2CH_3$) |
| **6m** | 84 | 103–104 | 8.26 (s, 1H, CH=), 8.13 (s, 1H, thiazolyl), 7.93 and 7.22 (d, 4H, $C_6H_4$), 7.75 (m, 2H, $H_{arom}$), 7.15 (d, 1H, $H_{arom}$) |