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# A multicomponent reaction efficiently producing arylmethylene 2-thiohydantoins☆

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**Abstract**—We describe here a multicomponent reaction that converts aryl/heteroaryl aldehydes efficiently into arylmethylene 2-thiohydantoins. 3-Formylindole behaves exceptionally giving a *gem*-diacetylthio derivative. A mechanistic study of the behaviour of 3-formylindole, which provides a new class of indole derivative, is described.


Synthetic enterprises are resource intensive with target molecules often needing an elaborate chain of separate reaction steps that may take weeks to complete. On an industrial scale huge amounts of raw materials and energy are required, often creating equal quantities of toxic waste. The average pharmaceutical synthesis yields 25–100 kg (including solvents) of waste per kilogram of product.[1]

One way to develop synthetic routes with excellent atom efficiency is to increase the number of reactions performed per pot, in the same way that metabolic pathways run many reactions in the same environment, that is to perform a multicomponent reaction.[1] Multicomponent reactions can use domino reactions or sequential reactions. Domino reactions describe closely coupled reactions where intermediates are inseparable, while in sequential reactions intermediates are separable.[2]

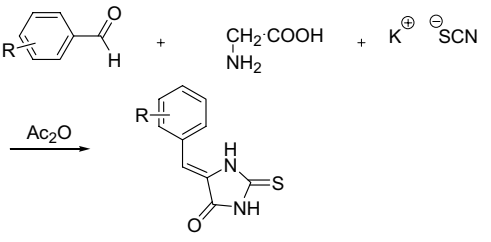
In a sequential reaction, the first step creates the conditions to trigger the next stage and that in turn sets up the third reaction, and so on. Hence, all the ingredients are added together at the beginning.[3]

We describe here a multicomponent reaction furnishing 2-thio analogues of arylmethylenehydantoin, a necessary component of many bioactive heterocycles,[4–7] in an efficient manner with the discovery of an unusual reaction of 3-formylindole.

A route reported in the literature to arylmethylene 2-thiohydantoins involves three steps with an overall yield of 41%.[4,8] Tedious distillation in step two and refluxing in all three steps makes it a time consuming and energy demanding process.

In our multicomponent synthesis of arylmethylene 2-thiohydantoins, we mixed glycine, potassium thiocyanate and an aryl/heteroaryl aldehyde, then added acetic anhydride and the mixture was stirred at rt (Scheme 1).

After 0.5 h all solid material had dissolved and an orange coloured solution was formed. The final compound precipitated out after 3–4 h of stirring (Table 1).




**Scheme 1.**

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†For crystallography queries.

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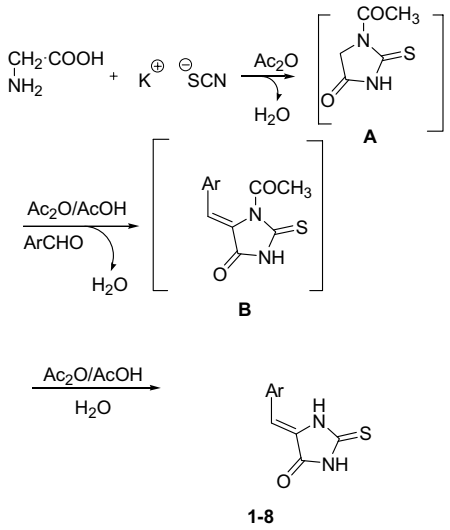
**Table 1.** Yields of arylmethylene 2-thiohydantoins obtained from the multicomponent procedure

| Product | Ar | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| **1** | 3-Pyridyl | rt[a] | 5 | 95 |
| **2** | 3-Furyl | rt | 4[b] | 94 |
| **3** | Phenyl | rt | 9 | 82 |
| **4** | 4-Pyridyl | rt | 4 | 80 |
| **5** | 2-Pyridyl | rt | 4 | 54[c] |
| **6** | 3-Thiophenyl | 60 | 5 | 64 |
| **7** | 4-Isopropylphenyl | 60 | 5 | 60 |
| **8** | 3-Benzyloxyphenyl | 60 | 5 | 76 |

[a] rt: room temperature, that is, 28–30 °C.
[b] See Supplementary data.
[c] Dimerization of the substrate occurs.

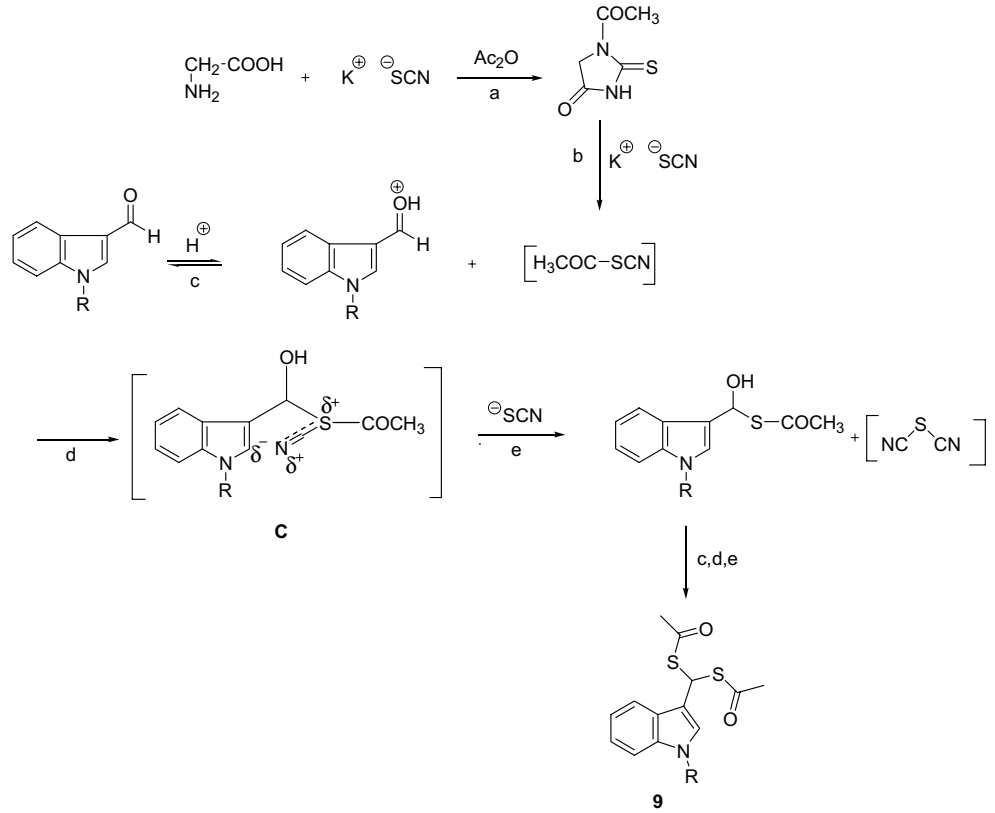
Three steps are involved (Scheme 2). Acetic anhydride promotes the cyclization to 1-acetyl-2-thiohydantoin **A**, with generation of one water molecule. The remaining acetic anhydride is sufficient to promote the condensation of the aldehyde, with the generation of another water molecule. Water hydrolyzes the acetic anhydride to generate acidic conditions, which leads to deacetylation of **B**. When the final product is insoluble in the reaction mixture, the reaction proceeds to completion (as in the case of unsubstituted aryl and heteroaryl aldehydes). This final deacetylation and formation of an insoluble product leads irreversibly to completion even at rt. The good to very good yields with unsubstituted and




**Scheme 2.**

**Table 2.** Yields of *gem*-diacetylthio indoles derivative **9**

| Product | R | Temp (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| **9a** | Methyl | 70 | 7 | 68 |
| **9b** | *n*-Butyl | 70 | 7 | 65 |
| **9c** | *p*-Cyanophenoxypentyl | 90 | 7 | 63 |




**Scheme 3a.** (a) Cyclization, (b) transfer acylation[12,13], (c) protonation, (d) attack of transient nucleophile and formation of intermediate **C**, (e) formation of hemithioacyl product.

3-substituted aryl/heteroarylaldehydes and comparatively lower yield in the case of 4-substituted arylaldehydes further support the proposed sequence of steps.

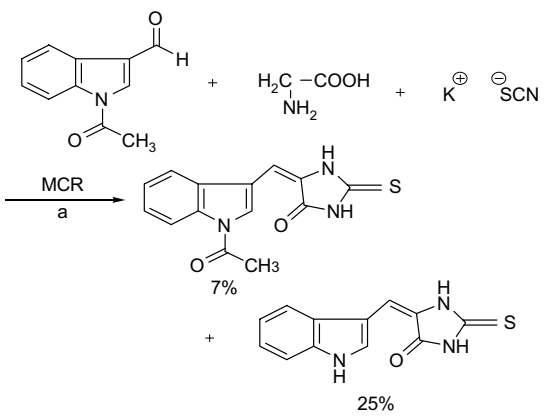
When 1-alkyl-3-formylindoles were utilized, 3-[1,1-bis(acetylthio)]indoles **9** were obtained (Table 2).

We searched the literature to find if such compounds were known and found that they had been prepared using thioacetic acid and sulfuric acid or polyphosphoric acid.[9,10]

There could be two explanations for this unusual behaviour of 3-formylindoles. Thioacetic acid might be generated in situ and then leads to *gem*-dithioacylation of the aldehyde. We reject this mechanism because other aldehydes would also be expected to react in the same way. Further, there is no report on the formation of thioacetic acid (ethanethioic acid) from acetic anhydride and potassium thiocyanate. We also followed the reaction course and found that initially, 1-acyl-2-thiohydantoin is generated and the final product formed when this is used up.

Hence, we propose another mechanism as shown in Scheme 3a. The 1-acyl-2-thiohydantoin acetylates the thiocyanate anion to generate acetylthiocyanate (at least transiently). This may not be a good nucleophile but stabilization of transition state **C** pushes the reaction in a forward direction. The high electron density at C-2 could be crucial for this behaviour. To prove this hypothesis, we performed the same reaction with a 1-acylated-3-formylindole, where the electron density at C-2 was less (as was evident from the $\delta$ value of H-2). We found no *gem*-dithioacylated product, but instead found the hydantoin product, however, in very low yield (Scheme 3b). Also, when we excluded glycine from the reaction mixture, no product was formed supporting transfer acylation of the thiocyanate anion to generate a sufficient amount of acetylthiocyanate. This experimental evidence best favours the mechanism proposed in Scheme 3a.

Figure 1 shows the ORTEP diagram of this unusually protected indole-3-carbaldehyde.[11] The mass spectra of all three compounds **9a**–**c** show a loss of fragment *m*/*e* 75 (–$SCOCH_3$), from the molecular ion.




**Scheme 3b.** (a) See Scheme 2.

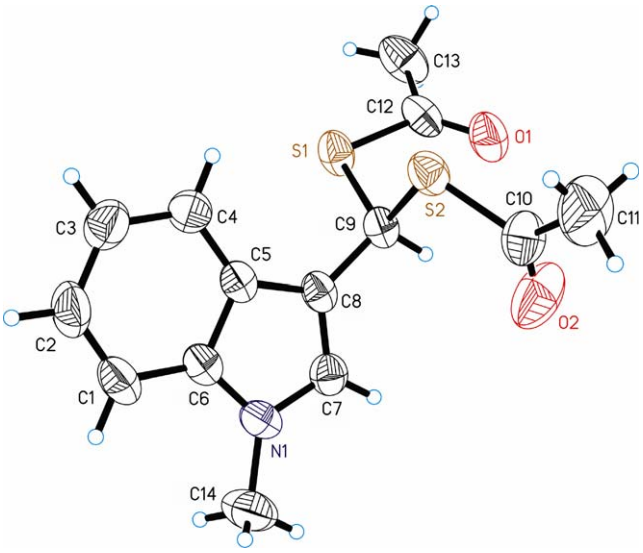



**Figure 1.** ORTEP diagram of **9** (R = Me), (at 50% probability level) showing the conformation of the molecule.

Since molecules **9a**–**c** possess thioester linkages[14,15] we submitted them for biological testing, with promising results. Further study of the biological activity of this class of molecules is currently ongoing.

In conclusion, we have developed an efficient method for synthesizing arylmethylene 2-thiohydantoins with aryl and heteroaryl aldehydes. A partial understanding of an unusual protection procedure for the aldehyde function of indoles also gives some insight into how we might generalize this novel *gem*-diacetylthio protection for any aldehyde.

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## Supplementary data

Experimental procedures for the preparation of compounds **1**–**9**, spectral data and scanned spectra for compounds **9a**–**c** are presented. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.076.

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11. *Crystal data for Compound* **9a**: $C_{14}H_{15}NO_2S_2$, $M = 293.39$, monoclinic, space group $P2_1/c$, $a = 10.897(1)$, $b = 8.357(1)$, $c = 16.747(2)$ Å, $\beta = 104.68(1)°$, $V = 1475.3(3)$ Å$^3$, $Z = 4$, $D_c = 1.321$ g cm$^{-3}$, $F(000) = 616.0$, $\mu = 0.36$ mm$^{-1}$, $\lambda$ (Mo $K_\alpha$) = 0.71073 Å, transparent block, crystal size $0.250 \times 0.225 \times 0.200$ mm, 3691 reflections measured ($R_{int} = 0.0230$), 2584 unique reflections, w$R2 = 0.0978$ for all data, conventional $R = 0.0376$ on $F$-values of 2092 reflections with $I > 2\sigma(I)$ and 0.0509 for all 2584 data, $S = 1.037$ for all data and 175 parameters. Unit cell determination and intensity data collection were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions were performed by direct methods and refinements by full-matrix-least-squares methods on $F^2$. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc., Madison, WI, USA, 1996], SHELXTL-NT [Bruker AXS Inc., Madison, WI, USA, 1997]. CCDC No. 297202 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (internat.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk.
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