



BF₃ etherate-mediated microwave-assisted facile synthesis of thiopyrano[2,3-*b*]indol-2-one



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ARTICLE INFO

Article history:

Received 4 October 2014
Revised 21 October 2014
Accepted 24 October 2014
Available online 30 October 2014

Keywords:

Indole
Indoline-2-thione
Thiocoumarine
Acetoacetic ester
Cyclization
Microwave-assisted synthesis

ABSTRACT

A facile synthesis of indole annulated 2*H*-thiopyran-2-ones has been developed by condensation of indoline-2-thiones with acetoacetic esters in the presence of borontrifluoride etherate (BF₃ etherate) using microwave irradiation. This one-step operationally simple methodology leads to thiopyrano[2,3-*b*]indol-2-ones in good yields.

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Heterocyclic compounds represent a large group of biologically active compounds,¹ which attract the attention of chemists from all around the world. In particular, the development of efficient and practical synthesis of indole annulated heterocycles is an active area of research in the current literature.² The interest is primarily driven by the growing volume of literature linking indole derivatives with a wide range of biological activities.³ Although, activities such as, anti-inflammatory, anti-bacterial, anti-hyperplasia, antipsychotic, analgesic, estrogen receptor modulators, and anti-cancer properties have been attributed to substituted thiopyrans and fused-thiopyran scaffolds, these *S*-containing heterocycles have not been explored to the same extent as their pyran counterparts.⁴ Certain indole annulated thiopyrans and their salts have been found to possess psychoanaleptic and nootropic effects as well as affinity toward aryl hydrocarbon receptor.^{5,6}

Microwave-assisted organic synthesis (MWOS) has rapidly evolved in the last decade as an efficient tool for synthetic chemists.⁷ Enhanced reaction rate, high yields, improved purity, and greener conditions make it an attractive technique for applications in the area of drug discovery and methodology development research. Considering the benefits of MWOS our group often exploits this tool in developing synthetic methodologies.^{8,9}

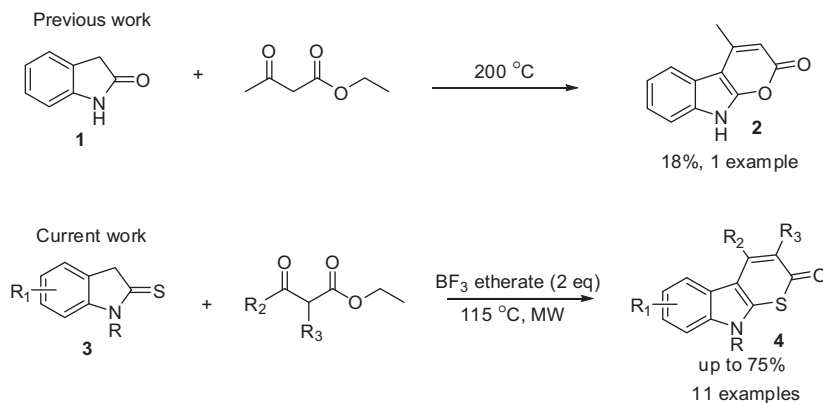
We have an ongoing interest in the development of novel strategies to access functionalized indoles.^{9–16} In an effort to chemically stitch these biologically relevant heterocycles (indole and thiopyran) together, we sought to develop a synthesis of thiopyrano[2,3-*b*]indol-2-one skeleton. Herein, we wish to report a microwave-assisted, BF₃ etherate-mediated, operationally simple, one-step synthesis of indole-annulated 2*H*-thiopyran-2-ones starting from indoline-2-thiones.

The Pechmann¹⁷-type condensation of indolin-2-one (**1**) with acetoacetic ester at 200 °C to produce 4-methylpyrano[2,3-*b*]indol-2-one (**2**) was reported by Nam and Grandberg in 2006.¹⁸ However, the yield of the product was found to be only 18% (Scheme 1). The fused-pyran skeleton **2** was recently synthesized in two steps from indolin-2-one via 3-acetyl-1*H*-indol-2-ols in decent yields.¹⁹ To the best of our knowledge, the synthesis of the thiopyran analog of **2**, that is, thiopyrano[2,3-*b*]indol-2-ones (**4**), has not been reported (Scheme 1).

Through our recent work on indolin-2-ones and indolin-2-thiones we have demonstrated that the latter is significantly more nucleophilic toward the substitution reactions involving these nuclei.^{14–16} Therefore, we envisaged that indoline-2-thione (**3**) would be an attractive candidate for the Pechmann-type condensation reaction compared to indolin-2-one (**1**) to produce thiopyrano[2,3-*b*]indol-2-ones (**4**) efficiently. Furthermore, in order to increase the efficacy of the reaction we were also interested in exploring the application of Lewis acids in the catalysis of the desired condensation reaction under MWOS conditions.

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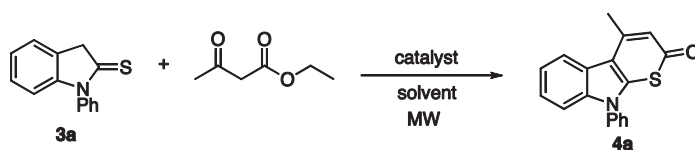
Scheme 1. Pechmann-type condensation using indolin-2-one (**1**) and indoline-2-thione (**3**).

In a test reaction, a mixture of 1-phenylindoline-2-thione (**3a**), ethyl acetoacetate (2 equiv), and a Lewis acid (BF_3 etherate, 1 equiv) was irradiated in a microwave reactor at 80 °C. The NMR analysis of the isolated product revealed the formation of 4-methyl-9-phenylthiopyrano[2,3-*b*]indol-2-one (**4a**) has been successful. Thus, we decided to systematically investigate this reaction in detail. Several substituted indolin-2-thiones **3a–f** were synthesized using a previously published procedure.²⁰ Acetoacetic esters were obtained from commercial sources. Initially, we chose *N*-phenylindoline-2-thione (**3a**) and ethyl acetoacetate as model reactants for the optimization of reaction conditions. As summarized in Table 1, the condensation reaction appears to be catalyzed by a variety of Lewis acids. Among the list of potential catalysts tested (CuOTf_2) was found to be the least effective in catalyzing the cyclization process (Table 1, entry 5). Compound **4a** was obtained in moderate yields using $\text{Eu}(\text{OTf})_3$, InBr_3 and $\text{Zn}(\text{OTf})_2$ (Table 1, entries 3, 7 and 8) in solvent toluene. However, the best conversion of **3a** to **4a** was achieved in the presence of excess of ethyl acetoacetate (5 equiv) and BF_3 etherate (2 equiv.) at 115 °C (Table 1, entry 9). Because the overall condensation results in the loss of a water molecule, the reaction efficacy was further improved with the use of molecular sieves (dehydrating agent) in

the reaction to absorb the liberated molecule of water (Table 1, entry 10). Interestingly, solvents appear to have a remarkable detrimental effect in the outcome of this reaction under microwave conditions, which could be caused due to the dilution of the reaction mixture. In general, all reactions carried out in solvents (toluene, DMF, acetonitrile and ethanol) resulted in poor yields of **4a** (Table 1, entries 2, 11–13). The presence of a Lewis acid was found to be essential for the transformation of **3a** to **4a** to take place. No conversion was observed in the absence of catalyst and only unreacted starting materials remained in the reaction (Table 1, entry 14). Therefore, after a thorough screening, the use of 2 equiv of BF_3 etherate with excess of ethyl acetoacetate (5 equiv) in the presence of molecular sieves and microwave irradiation for 10 min at 115 °C was established as an optimized condition for the conversion of **3a** to **4a**.

After optimizing the reaction conditions, we set out to demonstrate the substrate scope of the condensation reaction between indoline-2-thiones and acetoacetic esters. The results are illustrated in Table 2. In general, the condensation of *N*-alkylated indoline-2-thiones with simple acetoacetic esters resulted in higher yields of thiopyrans. The yields were compromised with the use of hindered acetoacetic esters. Higher temperature was required

Table 1
Optimization of reaction conditions for the synthesis of thiopyrano[2,3-*b*]indol-2-one **4a**



| Entry | Catalyst (mol %) | Solvent | Temperature (°C) | Time (min) | Yield ^a (%) |
|-----------|---|--------------|------------------|------------|------------------------|
| 1 | $\text{Zn}(\text{OTf})_2$ (20) | Toluene | 115 | 10 | 55 |
| 2 | BF_3 etherate (20) | Toluene | 115 | 10 | 30 |
| 3 | $\text{Eu}(\text{OTf})_3$ (20) | Toluene | 115 | 10 | 44 |
| 4 | $\text{La}(\text{OTf})_3$ (20) | Toluene | 115 | 10 | 32 |
| 5 | $\text{Cu}(\text{OTf})_2$ (20) | Toluene | 115 | 10 | >10 |
| 6 | InCl_3 (20) | Toluene | 115 | 10 | 40 |
| 7 | InBr_3 (20) | Toluene | 115 | 10 | 51 |
| 8 | BF_3 etherate (1 equiv) | — | 115 | 15 | 45 |
| 9 | BF_3 etherate (2 equiv) | — | 115 | 10 | 60 |
| 10 | BF_3 etherate (2 equiv)/mol sieves | — | 115 | 10 | 72 |
| 11 | BF_3 etherate (2 equiv) | DMF | 115 | 20 | >10 |
| 12 | BF_3 etherate (2 equiv) | Acetonitrile | 115 | 20 | >10 |
| 13 | BF_3 etherate (2 equiv) | Ethanol | 115 | 20 | 25 |
| 14 | No catalyst | Toluene | 115 | 20 | Nr ^b |

Bold values signify optimized reaction conditions.

^a Isolate yield.

^b nr = no reaction.

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