Microwave-promoted one-pot synthesis of 4H-thiopyrans from \(\alpha,\beta\)-unsaturated ketones via a three-component reaction

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Abstract—An efficient one-pot synthesis of substituted 4H-thiopyrans has been accomplished from a three-component reaction of \(\alpha,\beta\)-unsaturated ketones, Lawesson’s reagent and alkynes under microwave irradiation.

\(\text{Keywords: } \alpha,\beta\)-Unsaturated ketone; Thiopyran; Microwave; Lawesson’s reagent.

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The design of multi-component reactions (MCRs) is an important field of research from the point of view of combinatorial chemistry. Generally, multi-component reactions, being one-pot processes, afford good yields. They are fundamentally different from two-component reactions in several aspects because of advantages such as the simplicity of one-pot procedures, possible structural variations, complicated synthesis and large number of accessible compounds. The hetero Diels–Alder reaction of \(\alpha,\beta\)-unsaturated thioketones with activated dienophiles has been reported as an elegant strategy for 4H-thiopyran synthesis. However, the monomeric forms of the \(\alpha,\beta\)-unsaturated aliphatic thioketones, as such, are inaccessible because of their tendency to dimerize easily, even at low temperature. Generation of a monomeric thioketone usually necessitates either a stable thione dimer or dithione-type dimer as precursors. Nevertheless, these methods are disadvantageous due to the multiple reaction steps, prolonged reaction times and moderate yields. Our earlier efforts for the thionation of the conjugated ketone system of 16-dehydropregnenolone acetate (16-DPA) using P4S10 led to an adduct of 16-DPA-P2S5 which proved to be an efficient synthon for pyran synthesis as a masked conjugated enone. On the other hand our attempt to thionate 16-DPA with Lawesson’s reagent afforded 3\(\beta\)-acetoxy-2\(\beta\)-methyl-2\(\beta\)-thio-2\(\alpha\),4\(\alpha\),1\(\alpha\),3\(\beta\),2\(\beta\)-oxathiaporphiphino(16,17-d)androsten-5-ene which failed to participate in a [4+2]cycloaddition reaction with dienophiles under thermal conditions. Thus, thiopyran synthesis employing \(\alpha,\beta\)-unsaturated ketones in a one-pot reaction remained as an interesting goal.

The utility of microwave energy in synthetic organic chemistry has been increasingly recognized in recent years. Microwave-promoted solid phase heterogeneous reactions are environmentally benign methodologies having greater selectivity, enhanced reaction rates and produce cleaner products with manipulative simplicity. Microwave mediated multi-component reactions constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that products are formed in a single step and diversity can be achieved simply by varying the reacting components.

In continuation of our efforts towards multi-component reactions, we report herein a facile and rapid synthesis of 4H-thiopyrans from a three-component reaction of \(\alpha,\beta\)-unsaturated ketone, an alkyne and Lawesson’s reagent under microwave irradiation.

When a mixture of 1,3-diphenylprop-2-en-1-one 1a, Lawesson’s reagent (LR) and DMAD 2a was irradiated in a Synthewave 402 Prolabo focused microwave unit at a frequency of 2450 MHz (80% power) for 10 min, 2,3-bis(methoxycarbonyl)-4,6-diphenyl-4H-thiopyran 3a was obtained as an oil in 95% yield. The product was characterized by its spectroscopic and analytical data. The \(^1\)H NMR spectrum of 3a exhibited characteristic doublet proton signals at \(\delta = 6.09\) and 4.81 (J = 7.5 Hz) for the olefinic and methine protons, respectively. The \(^{13}\)C NMR spectrum showed ester carbonyl carbon signals at \(\delta = 166.06\) and 165.11 and the ESI mass spectra showed a molecular ion peak at m/z 389...
The cycloaddition reaction of 1a with alkynes 2b–d under identical conditions afforded thiopyrans 3b–h in 85–92% yields (Table 1, entries 2–8). Similarly, the three-component reaction of 16-dehydropregnenolone acetate 1e, LR and alkynes 2a–b gave high yields of the corresponding thiopyrans 3i–j (entries 9–10). However, our attempt to carry out the three-component reaction of 1a–d, LR and 2a–b under thermal conditions led to very poor yields of the products (3a–h) (Scheme 1).

In an effort to study the mechanism of the reaction, we attempted the [4+2]cycloaddition of 3b-acetoxy-20-(p-anisyl)-20-thio-60-methyl-20H,4,4'H-1',3',2'-oxathiaphosphino(16,17-d)androst-5-ene 6 with DMAD under microwave conditions. Despite its failure under thermal conditions (refluxing toluene), we observed that adduct A readily underwent [4+2]cycloaddition under microwave conditions to afford thiopyran 3i in high yield. The formation of 3i from A indicated its role as a precursor to the transient α,β-unsaturated thiketone monomer C. The mechanism is not yet clear, however, it is proposed that microwave heating facilitated conversion of A into C via concomitant rearrangement and ring opening reactions involving a tetracyclic oxophosphetane intermediate B (Scheme 2). In contrast to the

Table 1. Microwave-promoted one-pot preparation of 4H-thiopyrans 3 via the three-component reaction of conjugated ketones 1, LR and alkynes 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conjugated ketone</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Dienophile</th>
<th>R⁴</th>
<th>R⁵</th>
<th>Reaction time/min</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>2a</td>
<td>COOMe</td>
<td>COOMe</td>
<td>10</td>
<td>3a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>2b</td>
<td>COOEt</td>
<td>H</td>
<td>12</td>
<td>3b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>Ph</td>
<td>2a</td>
<td>COOMe</td>
<td>COOMe</td>
<td>10</td>
<td>3c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>p-ClC₆H₄</td>
<td>H</td>
<td>Ph</td>
<td>2b</td>
<td>COOEt</td>
<td>H</td>
<td>12</td>
<td>3d</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>2a</td>
<td>COOMe</td>
<td>COOMe</td>
<td>10</td>
<td>3e</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>Ph</td>
<td>H</td>
<td>p-MeOC₆H₄</td>
<td>2b</td>
<td>COOEt</td>
<td>H</td>
<td>12</td>
<td>3f</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>Me</td>
<td>H</td>
<td>Ph</td>
<td>2a</td>
<td>COOMe</td>
<td>COOMe</td>
<td>10</td>
<td>3g</td>
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<tr>
<td>8</td>
<td>1d</td>
<td>Me</td>
<td>H</td>
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<td>COOEt</td>
<td>H</td>
<td>12</td>
<td>3h</td>
<td>85</td>
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<tr>
<td>9</td>
<td>1e</td>
<td>Me</td>
<td>Androst</td>
<td>2a</td>
<td>COOMe</td>
<td>COOMe</td>
<td>12</td>
<td>3i</td>
<td>93</td>
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</tr>
<tr>
<td>10</td>
<td>1e</td>
<td>Me</td>
<td>Androst</td>
<td>2b</td>
<td>COOEt</td>
<td>H</td>
<td>12</td>
<td>3j</td>
<td>95</td>
<td></td>
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</table>

Scheme 1.
reaction of 1e with LR which gave A, under identical conditions, no oxathiophosphinino derivatives were obtained from chalcones 1a–d.

In conclusion, we have demonstrated a microwave-promoted one-pot synthesis of thiopyrans employing three-component reactions of α,β-unsaturated ketones, LR and alkylene dienophiles. Under microwave irradiation, the oxathiophosphinino derivative A could be readily converted to monomeric conjugated thioketone C which participated in the [4+2]cycloaddition reaction with alkynes. Our study supported the intermediacy of a six-membered oxathiophosphinino derivative during the process of thionation of conjugated ketones to thioketones. Further mechanistic study and generalization of the scope of this reaction is in progress.

Acknowledgements

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References and notes

12. Selected spectral and analytical data: Compound 3a, 1H NMR (300 MHz, CDCl3) δ 7.84 (1H, d, J = 8.0 Hz), 7.49 (1H, d, J = 7.5 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.13 (2H, d, J = 8.0 Hz) 7.02 (2H, d, J = 8.0 Hz), 6.95 (2H, d, J = 8.0 Hz) 6.67 (2H, d, J = 8.0 Hz) 6.83 (2H, d, J = 8.0 Hz) 6.67 (2H, d, J = 8.0 Hz) 6.44 (2H, d, J = 8.0 Hz) 6.20 (2H, d, J = 8.0 Hz) 5.96 (2H, d, J = 8.0 Hz) 5.41 (2H, d, J = 8.0 Hz) 5.36 (2H, d, J = 8.0 Hz) 5.14 (2H, d, J = 8.0 Hz) 4.78 (2H, d, J = 8.0 Hz).