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Microwave-promoted one-pot synthesis of 4*H*-thiopyrans from α,β-unsaturated ketones via a three-component reaction

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Abstract—An efficient one-pot synthesis of substituted 4*H*-thiopyrans has been accomplished from a three-component reaction of α,β-unsaturated ketones, Lawesson's reagent and alkynes under microwave irradiation.

The design of multi-component reactions (MCRs) is an important field of research from the point of view of combinatorial chemistry.[1] 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.[2] The hetero Diels–Alder reaction of α,β-unsaturated thioketones with activated dienophiles has been reported as an elegant strategy for 4*H*-thiopyran synthesis.[3] However, the monomeric forms of the α,β-unsaturated aliphatic thioketones, as such, are inaccessible because of their tendency to dimerize easily, even at low temperature.[4] Generation of a monomeric thioketone usually necessitates either a stable thione dimer or dithiine-type dimer as precursors.[5] 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 P_4S_{10} led to an adduct of 16-DPA-P_2S_5 which proved to be an efficient synthon for pyran synthesis as a masked conjugated enone.[6] On the other hand our attempt to thionate 16-DPA with Lawesson's reagent afforded 3β-acetoxy-2′-(*p*-anisyl)-2′-thio-6′-methyl-2′*H*,4′*H*-1′,3′,2′-oxathiaphosphinino(16,17-*d*)androst-5-ene which failed to participate in a [4+2]cycloaddition reaction with dienophiles under thermal conditions. Thus, thiopyran synthesis employing α,β-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.[7] Microwave-promoted solid phase heterogeneous reactions are environmentally benign methodologies having greater selectivity, enhanced reaction rates and produce cleaner products with manipulative simplicity.[8] 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.[9] In continuation of our efforts towards multi-component reactions,[10] we report herein a facile and rapid synthesis of 4*H*-thiopyrans from a three-component reaction of an α,β-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-4*H*-thiopyran **3a** was obtained as an oil in 95% yield.[11] The product was characterized by its spectroscopic and analytical data.[12] 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 δ 166.06 and 165.11 and the ESI mass spectra showed a molecular ion peak at *m*/*z* 389

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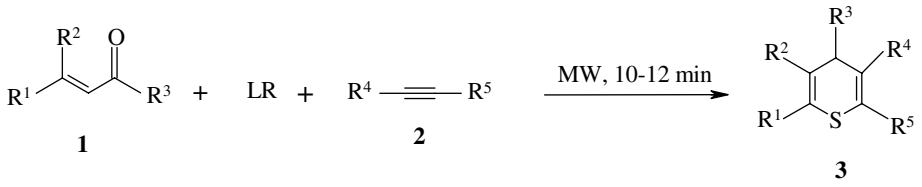
(M^++Na). The cycloaddition reaction of **1a** with alkynes **2b** and **1b–d** with **2a–b** under identical conditions afforded thiopyrans **3b–h** in 85–92% yields (Table 1, entries 2–8). Similarly, the three-component reaction of 16-dehydropregnenolone acetate **1e**, LR and alkynes **2a–b** gave 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).

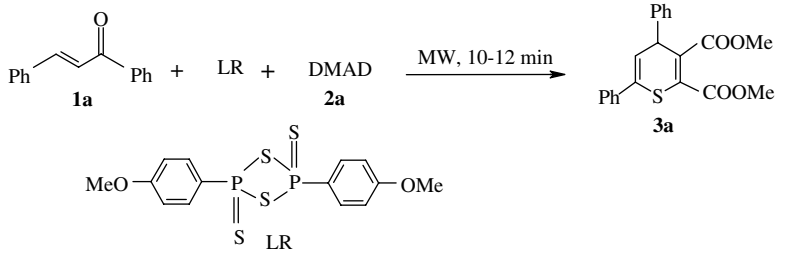
In an effort to study the mechanism of the reaction, we attempted the [4+2]cycloaddition of 3β-acetoxy-2′-(*p*-anisyl)-2′-thio-6′-methyl-2′*H*,4′*H*-1′,3′,2′-oxathiaphosphinino(16,17-*d*)androst-5-ene **A**[6] with DMAD under microwave conditions. Despite its failure under thermal conditions (refluxing 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 thioketone 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 4*H*-thiopyrans **3** via the three-component reaction of conjugated ketones **1**, LR and alkynes **2**

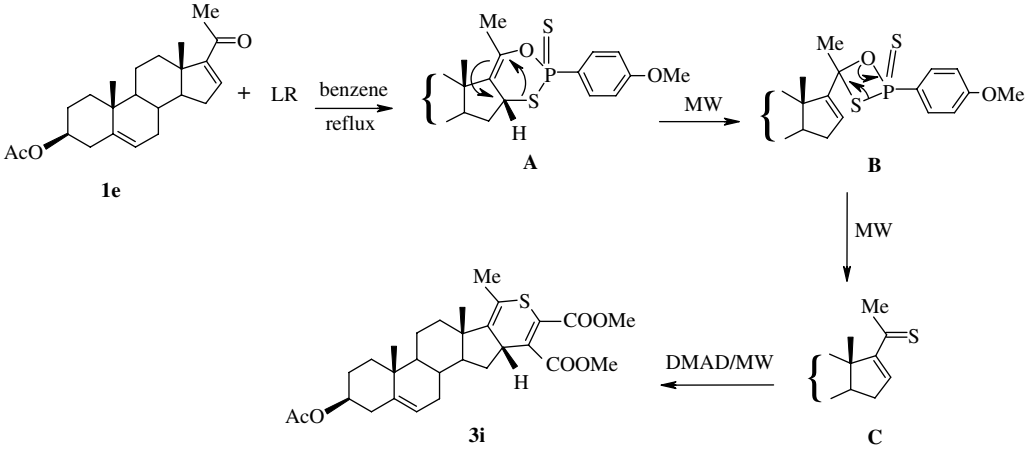


1 **2** **3**

Entry	Conjugated ketone	R^1	R^2	R^3	Dienophile	R^4	R^5	Reaction time/min	Product	Yield (%)
1	**1a**	Ph	H	Ph	**2a**	COOMe	COOMe	10	**3a**	95
2	**1a**	Ph	H	Ph	**2b**	COOEt	H	12	**3b**	90
3	**1b**	*p*-ClC_6H_4	H	Ph	**2a**	COOMe	COOMe	10	**3c**	92
4	**1b**	*p*-ClC_6H_4	H	Ph	**2b**	COOEt	H	10	**3d**	91
5	**1c**	Ph	H	*p*-$MeOC_6H_4$	**2a**	COOMe	COOMe	12	**3e**	90
6	**1c**	Ph	H	*p*-$MeOC_6H_4$	**2b**	COOEt	H	12	**3f**	88
7	**1d**	Me	H	Ph	**2a**	COOMe	COOMe	10	**3g**	87
8	**1d**	Me	H	Ph	**2b**	COOEt	H	10	**3h**	85
9	**1e**	Me	Androst		**2a**	COOMe	COOMe	12	**3i**	93
10	**1e**	Me	Androst		**2b**	COOEt	H	12	**3j**	95



Scheme 1.



Scheme 2.

reaction of **1e** with LR which gave **A**, under identical conditions, no oxathiaphosphinino 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 alkyne dienophiles. Under microwave irradiation, the oxathiaphosphinino 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 oxathiaphosphinino 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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12. Selected spectral and analytical data: Compound **3a**,[11] yield 95%, oil; IR ($CHCl_3$) ν 2951, 1733, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (10H, m), 6.09 (1H, d, $J = 7.5$ Hz), 4.81 (1H, d, $J = 7.5$ Hz), 3.79 (3H, s), 3.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.06, 165.11, 141.66, 136.73, 133.86, 130.78, 128.87 (3C), 128.64 (2C), 127.87 (3C), 127.51 (2C), 126.51, 120.59, 53.11, 52.37, 44.36; Mass spectra (ESI): m/z 389 (M^++Na). Compound **3c**, yield 92%, oil; IR ($CHCl_3$) ν 2970, 1733, 1721, 1263 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.24 (9H, m), 6.10 (1H, d, $J = 5.0$ Hz), 4.87 (1H, d, $J = 4.8$ Hz), 3.86 (3H, s), 3.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.06, 165.11, 141.66, 135.45, 135.11, 133.56, 130.09, 129.52, 129.44, 129.31, 128.87, 128.59 (2C), 127.88, 127.27 (2C), 126.51, 121.36, 53.11, 52.37, 44.36; Mass spectra (ESI): m/z 423 (M^++Na), 425 ([M^++Na] + 2). Compound **3e**, yield 90%, oil; IR ($CHCl_3$) ν 2951, 1739, 1727, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–6.94 (9H, m), 6.68 (1H, d, $J = 4.5$ Hz), 4.96 (1H, d, $J = 4.5$ Hz), 3.83 (3H, s), 3.78 (3H, s), 3.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.41, 166.99, 159.83, 148.10, 141.48, 136.83, 133.61, 129.85, 129.36, 129.08, 128.70 (2C), 128.59, 123.18, 128.20, 128.07, 123.18, 113.22, 55.24, 52.69, 51.36, 42.23; Mass spectra (ESI): m/z 419 (M^++Na). Compound **3g**, yield 87%, oil; IR ($CHCl_3$) ν 2952, 1732, 1727, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.23 (5H, m), 5.67 (1H, d, $J = 4.2$ Hz), 4.66 (1H, d, $J = 4.3$ Hz), 3.83 (3H, s), 3.62 (3H, s), 1.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.32, 165.40, 142.56, 134.11, 130.18, 128.99, 128.79, 128.02, 127.56, 127.28, 125.55, 120.24, 53.47, 52.70, 44.43, 22.01; Mass spectra (ESI): m/z 327 (M^++Na). Compound **3j**, yield 95%, oil; IR ($CHCl_3$) ν 2942, 1731, 1707, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, $J = 16$ Hz), 5.69 (1H, d, $J = 16$ Hz), 5.33 (1H, bs), 4.57 (1H, m), 4.12 (2H, q, $J = 6$ Hz), 2.13 (3H, s), 1.99 (3H, s), 1.24 (3H, t, $J = 6$ Hz), 0.98 (3H, s), 0.63 (3H, s), 2.55–0.95 (17H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.91, 164.20, 138.23, 127.54 (2C), 121.62, 119.56, 113.42, 72.36, 54.11, 52.62, 48.41, 48.02, 47.43, 36.53, 36.21, 34.86, 31.21, 30.84, 30.33, 26.28, 20.77, 20.10, 18.96, 17.82, 16.95, 16.20, 15.88; Mass spectra (ESI): m/z 493 (M^++Na).