

# A new approach to cyclohexenes and related structures

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Received (in Liverpool, UK) 9th February 2000, Accepted 25th February 2000

Published on the Web 15th March 2000

**Intermolecular radical addition of a xanthyl phosphonoacetate to a  $\gamma,\delta$ -enone gives rise to an adduct suitable for a base induced Horner–Emmons ring closure to a cyclohexene derivative, optionally after the reductive removal of the xanthate group.**

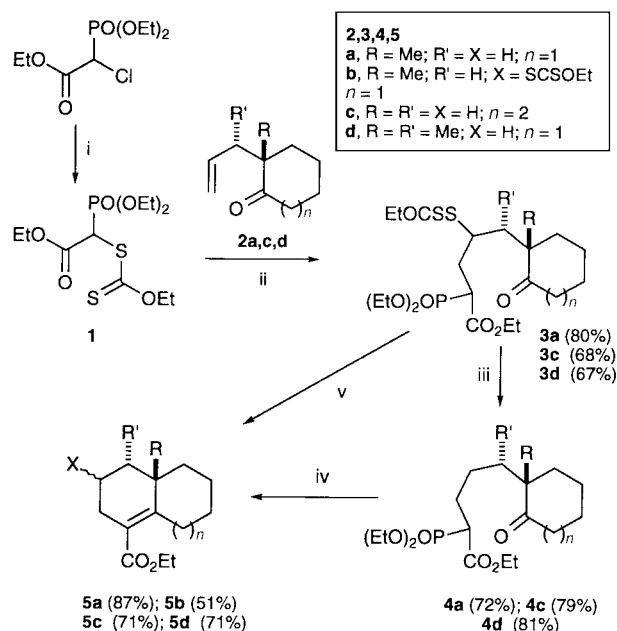
The construction of rings often hinges on the ability to attach together two reacting partners, which are then made to undergo an intramolecular combination under suitable conditions.<sup>1</sup> In some cases, such as in the classical Robinson annelation, both the attachment and cyclisation require similar reaction conditions and can sometimes be accomplished concomitantly. This, however, imposes various constraints in terms of selectivity that must be addressed.<sup>1b</sup> More frequently, one or both of the reacting functions have to be protected and then unmasked just before the cyclisation step. A more concise approach would be to combine an intermolecular assembly process with a ring closure proceeding through two different mechanisms and operating under orthogonal sets of conditions: the two reacting units are thus rapidly brought together whilst avoiding cumbersome protection–deprotection steps. In view of the importance of ring structures in essentially all classes of natural products, numerous combinations of reactions have therefore been exploited to construct mono- and poly-cyclic derivatives.<sup>1</sup> Here, we describe the use of an intermolecular radical addition to an unactivated olefin in conjunction with an intramolecular Horner–Emmons reaction to rapidly access various cyclohexene containing architectures.

Unlike intermolecular C–C bond formation involving radical additions to activated (usually electrophilic) olefins, clean bimolecular additions to simple alkenes are not generally easy to accomplish using common radical processes.<sup>2</sup> The rate of the addition step is often too slow to allow it to compete successfully with other pathways open to the radical intermediate. In stannane based chemistry for example, premature hydrogen abstraction from the organotin hydride is difficult to avoid.<sup>3</sup> This limitation may be lifted to a large extent by using the dithiocarbonate (xanthate) transfer reaction we have developed over the past few years.<sup>4</sup> The main competing pathway is degenerate: the intermediate radicals acquire an extended effective lifetime and are thus able to interact with comparatively unreactive traps. For our present purpose, the reaction of xanthate **1**<sup>5</sup> derived from triethyl phosphonoacetate with a  $\gamma,\delta$ -enone would provide in one step the desired combination of functionality for a subsequent intramolecular Horner–Emmons ring closure (Scheme 1). Indeed, heating 2-allyl-2-methylcyclohexanone **2a** (1.08 mmol) with xanthate **1** (2.17 mmol) in refluxing 1,2-dichloroethane (2 mL) in the presence of a small amount of lauroyl peroxide (16 mol%) as initiator under an inert atmosphere delivered the expected adduct **3a** in (80%) yield (Scheme 1). Reductive removal of the xanthate group with tributylstannane and base-induced (NaH/THF) cyclisation finally gave bicyclic derivative **5a** in high overall yield. The Horner–Emmons reaction may, if desired, be performed whilst keeping the xanthate group. In this way, **3a** was efficiently converted into **5b** by exposure to a combination of potassium carbonate and 18-crown-6 in toluene.<sup>6</sup> The initial NaH/THF system did not prove suitable in this case. The

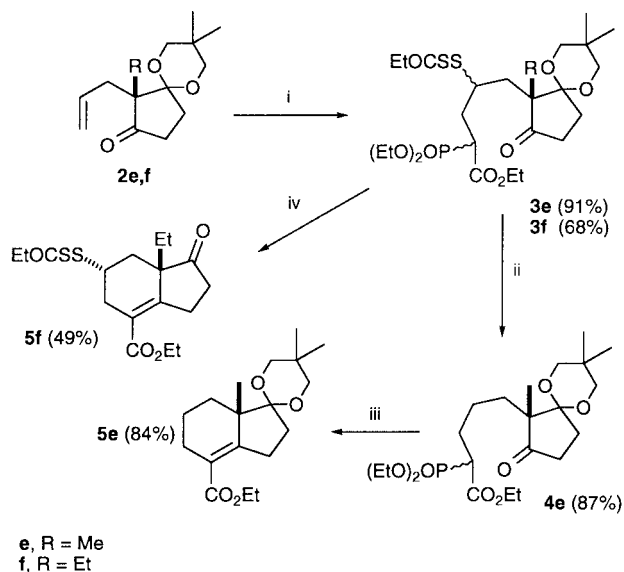
xanthate group in the final product represents a very useful handle since it provides an entry into the exceptionally rich chemistry of sulfur. The ring size of the starting cyclic ketone may of course be modified as illustrated by the conversion of cycloheptanone **2d** into bicyclo [5.4.0] derivative **5c**. Fused 6–7 ring systems are found in some terpene families, such as the sandresolides, the tiglanes (e.g. phorbol), and the daphnanes.<sup>7</sup>

One important feature of this approach is that the unsaturated ketone precursors are readily available, either by direct allylation of the corresponding enolate or through the powerful Claisen rearrangement. The latter route is especially interesting, since it can provide substituted substrates with controlled relative (and sometimes absolute) stereochemistry of adjacent chiral centres.<sup>8</sup> Compound **2d** was thus obtained by heating together 1-methoxy-2-methylcyclohexene and crotyl alcohol in the presence of trifluoroacetic acid.<sup>8</sup> Application of the same sequence gave **5d** with a defined relative stereochemistry, again in good overall yield (Scheme 1).

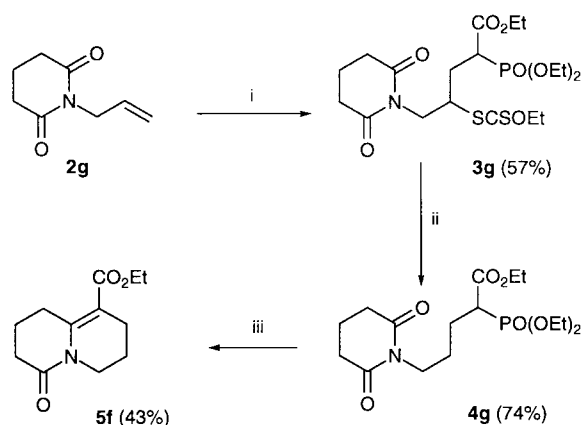
If a 2-allyl cyclopentanedione component is employed, the sequence now provides a ready access to the ubiquitous hydrindane backbone. This is illustrated by the conversion of **2e**, prepared by allylation of 2-methylcyclopentane-1,3-dione with allyl bromide<sup>9</sup> followed by ketalisation of one of the ketone groups, into **5e**, as outlined in Scheme 2. This route is significantly shorter than that previously reported for an analogue of **5e**.<sup>10</sup> The presence of the olefin allows access to the *trans*-hydrindane system through catalytic reduction.<sup>10</sup> For the ethyl derivative **2f**, the Horner–Emmons reaction was performed after acid mediated cleavage of the ketal group but



**Scheme 1** Reagents and conditions: i, EtOCSSt, acetone; ii, lauroyl peroxide (0.1–0.2 equiv.), 1,2-dichloroethane, reflux; iii, Bu<sub>3</sub>SnH (AIBN), toluene, reflux; iv, NaH, THF; v, K<sub>2</sub>CO<sub>3</sub>/18-crown-6, toluene, reflux.



**Scheme 2** Reagents and conditions: i, lauroyl peroxide (10–20 mol%) cyclohexane, reflux; ii,  $\text{Bu}_3\text{SnH}$  (AIBN), toluene, reflux; iii, NaH, THF; iv, (a) *p*-TSA, acetone; (b)  $\text{K}_2\text{CO}_3/18\text{-crown-6}$ , toluene, 80 °C.



**Scheme 3** Reagents and conditions: i, lauroyl peroxide (8 mol%), 1,2-dichloroethane, reflux; ii, lauroyl peroxide (1.46 mol. equiv.), isopropyl alcohol, reflux; iii, NaH (4.0 equiv.), THF, reflux.

without removal of the xanthate. Ring closure took place only on the ketone group leading to the least congested isomer, **5f**, with the xanthate in the equatorial orientation and in a location corresponding to the important C-11 position in steroids. There are several clinically useful steroid drugs with the unnatural C-13 ethyl group and some, such as the third-generation contraceptive Desogestrel, also contain a substituent at C-11.<sup>11</sup> Surprisingly, a Robinson-type annulation to construct the C-ring in this series was recently reported to fail.<sup>12</sup>

Finally, the possibility of performing a non-classical Horner–Emmons reaction<sup>13</sup> on an imide may be exploited as an entry to indolizidine and quinolizidine alkaloids. An example of the

latter is displayed in Scheme 3. Addition of xanthate **1** to *N*-allylglutarimide followed by removal of the xanthate group using lauroyl peroxide/isopropyl alcohol gave the requisite adduct **4g** in 42% overall yield. We have previously described the use of this reagent combination as an economical and ecologically more acceptable alternative to organotin hydrides for reductively removing xanthates and related groups.<sup>14</sup> Treatment of **4g** with NaH/THF induced ring closure to furnish **5g** in 43% yield. This compound is in principle an immediate precursor of lupinine.<sup>15</sup> The moderate yield in the cyclisation step must be contrasted with the sole literature precedent of a Wittig–Horner-type cyclisation on a glutarimide motif, reported to proceed in only 19%.<sup>16</sup>

In summary, we have described a new, short and flexible strategy for accessing cyclohexenes and related structures. The key radical addition to the unactivated terminal olefin occurs under mild, *neutral* conditions, that are compatible with most functional groups encountered in modern synthesis.

We thank Dr Philippe Mackiewicz (Aventis, Romainville, France) for a generous gift of 2-ethylcyclopentane-1,3-dione.

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Communication b001119n