A General Synthesis of 2-Substituted Cyclohex-2-enones

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A new synthesis of 2-substituted cyclohex-2-enones has been achieved using a sequence involving the aldol reaction of the aluminium enolate derived from thiolate addition to cyclohex-2-enone, followed by dehydration, rearrangement and desulfurisation.

As part of a proposed alkaloid synthesis we required a method for the preparation of 2-substituted cyclohex-2-enones from cyclohex-2-enone and aldehydes (Fig. 1). Although a search of the literature revealed several possible methods for achieving this transformation,[1] our desired C-2 side chain was incompatible with strategies involving deoxygenation and/or acidic reaction conditions. A potential strategy, however, was suggested by the work of Levin in the prostaglandin field.[2]

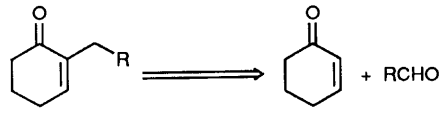
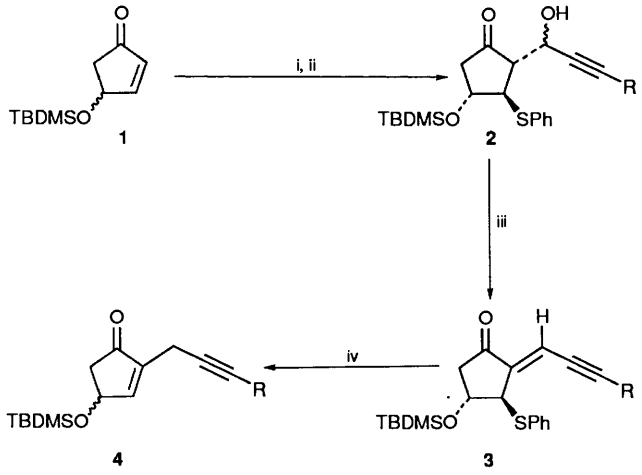


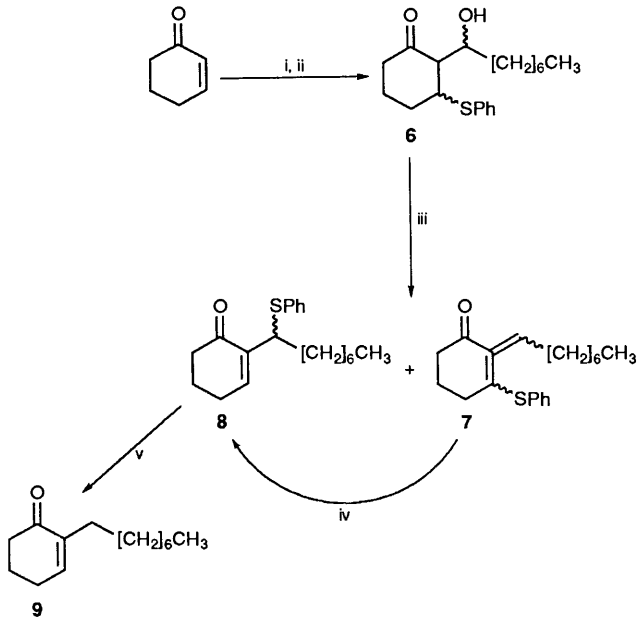
Fig. 1

In this approach the aluminium enolate derived from the cylopentenone **1** was treated with the prop-2-ynylic aldehyde **5** and the resulting mixture of aldol diastereoisomers **2** was dehydrated to give the enone **3**. Treatment of **3** with zinc in acetic acid–propan-2-ol afforded the 2-substituted cyclopentenone **4** by conjugate reduction followed by β-elimination of thiophenol (Scheme 1).[2]



Scheme 1 *Reagents and conditions:* (for R = $[CH_2]_3CO_2Me$) i, Me_2AlSPh, CH_2Cl_2, −78 °C; ii, $OHCCC[CH_2]_3CO_2Me$ **5**, THF, −78 °C; iii, $MeSO_2Cl$, pyridine, 0 °C; iv, Zn, AcOH, Pr^iOH, 25 °C

To investigate the viability of this chemistry for our alkaloid synthesis we treated the aluminium enolate derived from cyclohex-2-enone with octanal and obtained the desired aldol product **6** as a mixture of diastereoisomers in 36% yield (Scheme 2). Subjecting **6** to the conditions used by Levin effected only partial dehydration, however, utilising triethylamine as the base and performing the reaction in dichloromethane lead to the consumption of all the starting material, giving a mixture of isomeric products in 62% yield. Surprisingly, in addition to the expected (*E*) and (*Z*) enones **7** a substantial



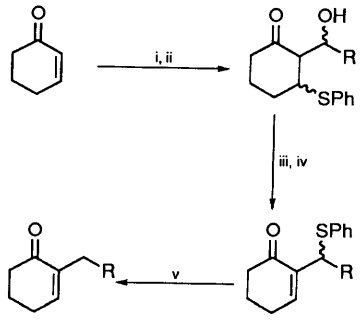
Scheme 2 *Reagents and conditions:* i, Me_2AlSPh, CH_2Cl_2, −78 °C; ii, $OHC[CH_2]_6CH_3$, THF, −78 °C; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C; iv, SiO_2, CH_2Cl_2, 25 °C; v, Raney nickel, EtOH, 25 °C

amount of the regioisomeric allylic sulfide **8** was observed. Attempted chromatographic separation of the allylic sulfides **7** and **8** met with partial success, pure isomer **8** was obtained, but **7** was contaminated with **8**. Repurification of this mixture gave a similar result. We speculated, therefore, that isomerisation of **7** to **8** was occurring during chromatography. Indeed, stirring the mixture of **7** and **8** in dichloromethane in the presence of silica gel overnight resulted in complete isomerisation, **8** being obtained in 55% yield from **6** (Scheme 2).

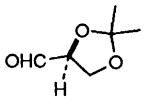
Although **7** could not be obtained in a sufficiently pure state to evaluate the Levin protocol we recognised, however, that desulfurisation of **8** would achieve our overall synthetic goal. Indeed, treatment of **8** with Raney nickel in ethanol at room temperature gave a 91% yield of 2-octylcyclohex-2-enone. This material was identical in all respects with the previously reported compound.[3] Although treatment of the crude mixture of allylic sulfides **7** and **8** with Raney nickel afforded only the desired isomer **9**, thus suggesting the intermediacy of a common allylic radical, the yield was inferior to the two-step procedure.

Having established this methodology for use in our proposed alkaloid synthesis we explored the generality of this novel synthetic sequence. The results are shown in Table 1. All the aldehydes investigated gave reasonable overall yields (unoptimised) of the corresponding 2-substituted cyclohex-2-enones. Satisfactory spectroscopic and HRMS data were obtained for all new compounds reported.

Table 1 Synthesis of 2-substituted cyclohex-2-enones



Reagents and conditions: i, Me_2AlSPh, CH_2Cl_2, −78 °C; ii, RCHO, THF, −78 °C; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 °C; iv, SiO_2, CH_2Cl_2, 25 °C, 16 h (SiO_2, $CHCl_3$, reflux, 4 days for R = Ph); v, Raney nickel, EtOH, 25 °C

	Yield (%)		
RCHO	Steps i and ii	Steps iii and iv	Step v
MeCHO	65	51	67
$CH_3[CH_2]_6CHO$	36	55	91
PhCHO	58	63	74
	56	64	63

Experimental

2-(1-*Hydroxyoctyl*)-3-*phenylsulfanylcyclohexanone* **6**.—To a stirred solution of thiophenol (4.41 g, 40.0 mmol) in dichloromethane (40 cm^3) at 0 °C under dry nitrogen was added trimethylaluminium (2.0 mol dm^{-3} solution in hexanes; 20 cm^3, 40.0 mmol) over 5 min. Stirring was continued for 30 min and then the clear solution cooled to −78 °C. A solution of cyclohex-2-enone (3.20 g, 33.3 mmol) in dichloromethane (40 cm^3) was added over 5 min, the mixture stirred at −78 °C for 1 h and then tetrahydrofuran (200 cm^3) added at such a rate as to maintain the temperature below −70 °C. Stirring was continued at −78 °C and then a solution of octanal (5.13 g, 40.0 mmol) in dry tetrahydrofuran (40 cm^3) was added over 5 min. After stirring at −78 °C for 3 h the reaction mixture was diluted with ethyl acetate (400 cm^3) and poured into 2 mol dm^{-3} hydrochloric acid (100 cm^3). The mixture was shaken, the layers separated, and the organic phase washed with brine (100 cm^3) followed by distilled water (100 cm^3). After drying ($MgSO_4$) the solvent was removed under reduced pressure to give a pale yellow oil (12.75 g) which was subjected to flash chromatography on SiO_2. This procedure afforded the title compound as a mixture of diastereoisomers (3.95 g, 36%) (Found: M, 334.1966. $C_{20}H_{30}O_2S$ requires *M*, 334.1967); ν_{max}(neat)/cm^{-1} 3450, 2930, 2860, 1710, 1440, 750 and 695; δ_H(270 MHz; $CDCl_3$) 0.87 (3 H, t, CH_3), 1.28 (10 H, m, octyl CH_2s), 1.42–2.45 [9 H, m, CH(OH)CH_2 + ring 2-H, 4-H_2, 5-H_2 and 6-H_2], 3.54 (1 H, m, ring 3-H), 4.05–4.26 [1 H, m, C*H*(OH)] and 7.28–7.50 (5 H, m, phenyl Hs); *m/z* (Cl) 352 ($M^+ + NH_4$, 3%), 335 (M^+ + H, 3), 224 (30), 207 (32), 114 (100) and 97 (88).

2-(1-*Phenylsulfanyloctylcyclohex*-2-*enone* **8**.—To a stirred mixture of **6** (3.0 g, 9.0 mmol), triethylamine (15 cm^3, 108.0 mmol) and dichloromethane (30 cm^3) maintained at 0 °C under dry nitrogen was added methanesulfonyl chloride (2.85 cm^3, 36.9 mmol) over 5 min. The resulting mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and the precipitated solid collected by filtration. Silica gel (5.0 g) was added to the filtrate and the mixture stirred at 25 °C for 16 h. The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give the title compound as a pale yellow oil (1.55 g, 55%) (Found: M, 316.1855. $C_{20}H_{28}OS$ requires *M*, 316.1861); ν_{max}(neat)/cm^{-1} 2925, 2860 and 1680; δ_H($CDCl_3$; 270 MHz) 0.87 (3 H, t, CH_3), 1.25 (10 H, m, octyl CH_2s), 1.66 [2 H, m, CH(SPh)CH_2], 1.93 (2 H, m, ring 5-H_2), 2.33 (2 H, m, ring 4-H_2), 2.42 (2 H, m, ring 6-H_2), 4.35 [1 H, t, C*H*(SPh)], 6.80 (1 H, t, ring 3-H) and 7.20–7.34 (5 H, m, phenyl Hs); *m/z* (EI) 316 (M^+, 37%) and 207 (100).

2-*Octylcyclohex*-2-*enone* **9**.—To a stirred solution of **8** (100 mg, 0.32 mmol) in absolute ethanol (0.5 cm^3) under dry nitrogen was added a slurry of W-2 grade Raney nickel in absolute ethanol, in approx 100 mm^3 portions until TLC indicated complete consumption of the starting material. The mixture was filtered under a nitrogen blanket and the nickel residue washed with dichloromethane (10 cm^3). The combined filtrates were washed with 2 mol dm^{-3} HCl (2 cm^3), dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. The residue was purified by bulb-to-bulb distillation to give a colourless oil (60 mg, 91%). This material was identical in all respects with the previously reported compound.[3]

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