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Acetylcyclopropane as a Five-carbon Building Block in the Synthesis of Acetogenin Transoid Insect Pheromones

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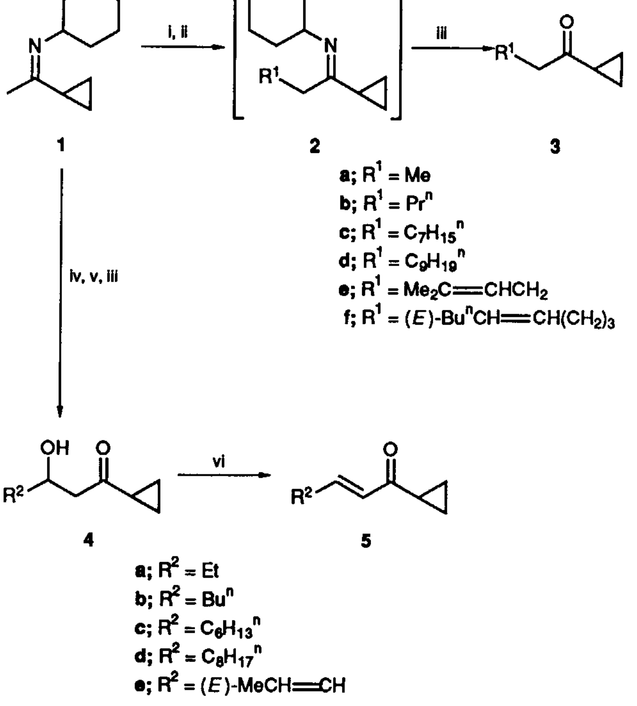
Controlled alkylation of deprotonated *N*-cyclohexyl-1-cyclopropylethylidene imine **1** or its condensation with aldehydes lead efficiently to the saturated (**3**) or conjugated (**5**) cyclopropyl ketones respectively, the latter being key intermediates in short stereospecific syntheses of some transoid Lepidoptera insect pheromones.

Alkyl- and alk-1-enyl-cyclopropyl ketones are attractive intermediates in organic synthesis.[1–3] Our own interest in these compounds as effective precursors of the transoid pheromones of a number of Lepidoptera insects is demonstrated by a recently developed method for their preparation starting from readily available acetylcyclopropane.[3,4] Here we describe an easy route from the latter in its cyclohexyl imine form **1** to the above carbonyl compounds by means of either alkylation or aldol-type condensation (Scheme 1). The data obtained further illustrate the applicability of acetylcyclopropane as a versatile and multipurpose five-carbon building block.



Scheme 1 *Reagents and conditions*: i, $\mathrm{Bu^nLi}$, THF–HMPA–hexane, $-70 \rightarrow 0$ °C, 1 h; ii, $\mathrm{R^1X}$ (**a**: X = I, **b–d**, **f**: X = Br, **e**: X = Cl), THF, $-70 \rightarrow 25$ °C, 2 h; iii, silica gel, without solvent, 25 °C, 15 min; iv, LDA, THF–HMPA–hexane, $-30 \rightarrow 0$ °C, 1 h; v, $\mathrm{R^2CHO}$, THF, $-70 \rightarrow 5$ °C, 20 min; vi, TsOH (cat.) (Ts = tosyl), $\mathrm{C_6H_6}$, 80 °C, 20 min

Table 1 Conversion of imine **1** into ketones **3–5**

	Boiling point/°C/mm Hg (% yield)		
	3	**4**	**5**
a	128/760(87)	97/10(72)	65/7(90)
b	73/20(84)	98/1(76)	59/1(91)
c	74/1(89)	90/0.07(76)	101/1(91)
d	102/1(88)	101/0.03(82)	85/0.03(92)
e	66/2(80)	81/1(58)[a]	67/1(96)
f	80/0.04(89)		

[a] Thermally sensitive compound.

Treatment of a tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA) (10:1) solution of **1**[5] with n-butyllithium (~ 1 mol equiv.) and subsequently with different alkyl halides (RX) (~ 1 mol equiv.) led to the respective alkylated products **2**. The crude imines **2** on short exposure with 3/4-fold (w/w) of silica gel in the 'dry state'[6] followed by flash chromatography of the reaction mixture over the same adsorbent furnished the ketones **3** in ~ 90% yield. In contrast, the ketone yield never exceeded 50% when the standard procedures for imine hydrolysis were employed.

Similar reaction sequences with the imine **1**, lithium diisopropylamide (LDA), and several aldehydes ($\mathrm{R^2CHO}$) smoothly afforded the *β*-hydroxy ketones **4**. Their dehydration in boiling benzene in the presence of TsOH as catalyst proceeded almost quantitatively to give the conjugated cyclopropyl ketones **5** (Table 1). It is noteworthy that the deprotonated imine **1** interacts regiospecifically with the above electrophiles at the methyl group in both cases.[†]

The compounds **3b–d**, **f** and **5a–e** have recently been recognized as key intermediates in the synthesis of acetogenin transoid pheromones.[3,4] Following a similar strategy the satur-

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[†] The new compounds **4** furnished satisfactory spectral (IR, NMR, mass) and microanalytical data.

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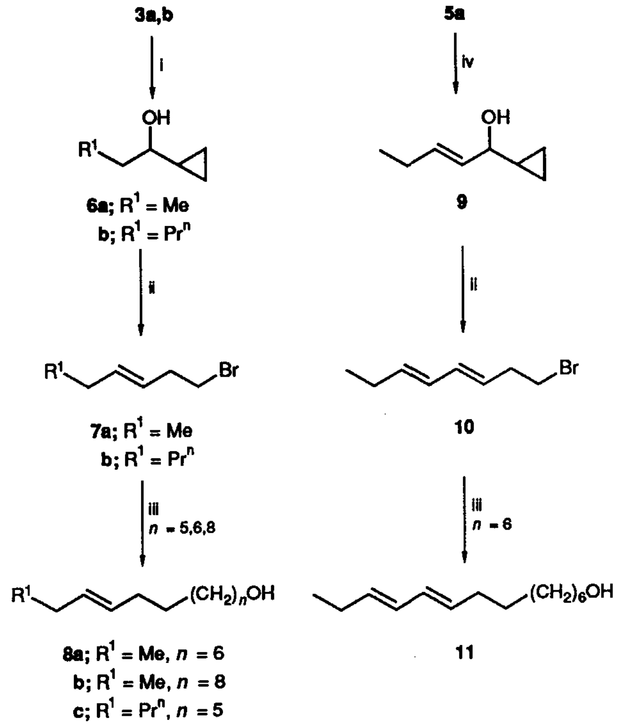

Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, 0 °C, 10 min, > 90%; ii, Me_3SiBr, $ZnBr_2$ (cat.), CH_2Cl_2, − 20 °C, 30 min, ~ 80%; iii, $BrMg(CH_2)_nOMgBr$ ($n = 5, 6, 8$), Li_2CuCl_4 (cat.), THF, − 70→25 °C, 2 h, 60–70%; iv, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, − 20 °C, 10 min, 84%

ated (**3a**, **b**) and conjugated (**5a**) cyclopropyl ketones obtained by our novel methodology were employed in a short synthesis of some other representatives of the series (Scheme 2).

Thus, the cyclopropyl alcohols **6a**, **b**, readily available by hydride reduction of **3a**, **b**, were treated with trimethylsilyl bromide and a catalytic amount of $ZnBr_2$ following our reported procedure[3] to give the rearranged (*E*)-homoallyl bromides **7a**, **b** in high yields. Their subsequent coupling with Grignard reagents prepared from the α,ω-bromoalkanols $Br(CH_2)_nOH$ in the presence of Li_2CuCl_4[7] led smoothly to the target primary alcohols **8a–c**. Similarly, a three-stage synthesis of the dienol **11** was performed *via* the intermediate allylic alcohol **9** and the homoallylic bromide **10**, the former being obtained by $CeCl_3$ induced[8] borohydride reduction of the starting ketone **5a**.

The alcohols **8** and **11** and/or their acetates are known to constitute pheromonal components for more than 30 species of Lepidoptera insects.[9] Thus alkyl- and vinyl-cyclopropyl ketones, readily available from acetylcyclopropane, serve as valuable intermediates in regio- and stereo-specific synthesis of some acetogenin insect pheromones.

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References

1 H. N. C. Wong, M.-Y. Hon, C.-W. Tse and Y.-C. Yip, *Chem. Rev.*, 1989, **89**, 165; R. A. Myrsina and N. V. Kuznetsov, *Ukr. Khim. Zh., Russ. Ed.*, 1976, **42**, 407 (*Chem. Abstr.*, 1976, **85**, 20649b); R. T. Hrubiec and M. B. Smith, *J. Org. Chem.*, 1984, **49**, 431; M. C. Aploim, A. D. Morris, W. B. Motherwell and D. M. O'Shea, *Tetrahedron Lett.*, 1988, **29**, 4173; O. Tsuge, S. Kanemasa, T. Otsuka and T. Suzuki, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2897; S. Kanemoto, M. Shimizu and H. Yoshioka, *J. Chem. Soc., Chem. Commun.*, 1989, 690.

2 K. Mori, *Tetrahedron*, 1972, **28**, 3747.

3 A. M. Moiseenkov, B. A. Czeskis, N. M. Ivanova and O. M. Nefedov, *Org. Prep. Proced. Int.*, 1990, **22**, 215; B. A. Czeskis, N. M. Ivanova, A. M. Moiseenkov and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1190, 2025.

4 B. A. Czeskis, N. M. Ivanova, A. M. Moiseenkov and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2539; N. M. Ivanova, B. A. Czeskis, E. V. Rubanova, V. G. Yatzynin, A. M. Moiseenkov and O. M. Nefedov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991(3), in the press.

5 W. Coppens and N. Schamp, *Bull. Soc. Chim. Belg.*, 1972, **81**, 643.

6 V. V. Veselovsky, A. S. Gybin, A. V. Lozanova, A. M. Moiseenkov and V. A. Smit, *Tetrahedron Lett.*, 1988, **29**, 174; R. B. Mitra and G. B. Reddy, *Synthesis*, 1989, 694.

7 M. Tamura and J. Kochi, *Synthesis*, 1971, 303.

8 S. Fukuzawa, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1929.

9 H. J. Bestmann and O. Vostrowsky, in *Chemie der Pflanzenschutz und Schadlingsbekamphungsmittel*, vol. 6, ed. R. Wegler, Springer-Verlag, Berlin, Heidelberg, New York, 1981, p. 29; R. Baker and J. W. S. Bradshaw, *Aliphatic Relat. Nat. Prod. Chem.*, 1983, 3, 66; R. Baker and R. H. Herbert, *Nat. Prod. Rep.*, 1984, **1**, 299; P. J. Silk, E. W. Butterworth, L. P. S. Kuenen, C. J. Northcott and E. G. Ketella, *J. Chem. Ecol.*, 1988, **14**, 1417; G. C. Lonergan, B. M. Ponder, W. D. Seabrook and L. R. Kipp, *J. Chem. Ecol.*, 1989, **15**, 2495; S. Muggleston and S. P. Foster, *Physiol. Entymol.*, 1989, **14**, 443.