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A novel one-step efficient method for the synthesis of tetrahydroindoles from 1-(1-pyrrolidino)cyclohexene and chloropyruvates

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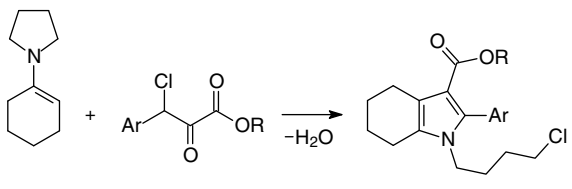
ABSTRACT

A highly efficient, one-step, versatile method for the synthesis of tetrahydroindoles has been developed on the basis of new ring formation in the reactions of 1-(1-pyrrolidino)cyclohexene with chloropyruvates.

Indoles are one of the most widespread heterocyclic compounds in Nature. The total number of known indole alkaloids is ca. 1500.[1] The potent physiological properties of many of them have led to their use in medicine, but in most instances, they have at present to be supplanted by synthetic substances.[2] Natural indole alkaloids applicable in medicine are varied, and it is not always possible to obtain their synthetic analogues using known methods for indole synthesis. This appears to be the reason why the numerous known reactions, beginning with the classical Fischer reaction,[3] refer to the synthesis of indole derivatives, most of these reactions having been discovered only recently. Some of these methods[4–8] are suitable for the synthesis of indole derivatives with substituents on the carbon atoms of the five-membered ring, whilst others[9,10] are convenient for indoles with substituents on the carbon atoms of the six-membered ring. Other methods [11,12] are used successfully for the synthesis of indole derivatives with substituents on the carbon atoms of both rings of the indole. However, a method for producing indole derivatives with substituents on both the carbon and the nitrogen atoms of the five-membered ring is not available in the literature.

In this Letter, a direct, efficient and operationally convenient approach to the synthesis of 1,2 and 3-substituted tetrahydroindoles based on the cascade reactions of 1-(1-pyrrolidino)cyclohexene **1** and chloropyruvates[13] is presented. The tetrahydroindoles obtained according to this approach can be transformed easily into various tetrahydroindole derivatives (Scheme 1).

Despite the well-known chemistry of enamines[14] in general, and of 1-(1-pyrrolidino)cyclohexene[15] **1** in particular, the reaction of the latter with chloropyruvates appears not to proceed via initial nucleophilic substitution of the halogen atom in these highly electrophilic compounds, but via nucleophilic addition to the carbonyl group. This is followed by cascade conversions involving (a) an intramolecular nucleophilic substitution of the S_N2 type with the formation of an epoxide ring and elimination of Cl^-, (b) opening of the pyrrolidine ring on exposure to Cl^-, see Scheme 2, **A**, (c) imino-enamine tautomerism **B**⇄**C**, (d) opening of the epoxide ring



1 **2** **3**

2,3	Ar	R	% yield of 3	2,3	Ar	R	% yield of 3
a	Ph	Me	85	**e**	4-$O_2NC_6H_4$	Me	90
b	Ph	Et	77	**f**	3-$O_2NC_6H_4$	Me	80
c	Ph	Pr-*i*	72	**g**	4-ClC_6H_4	Me	70
d	Ph	Pr-*n*	80	**h**	4-BrC_6H_4	Me	74

Scheme 1.

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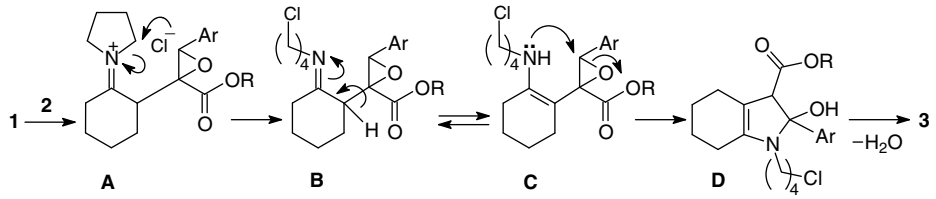


Scheme 2.

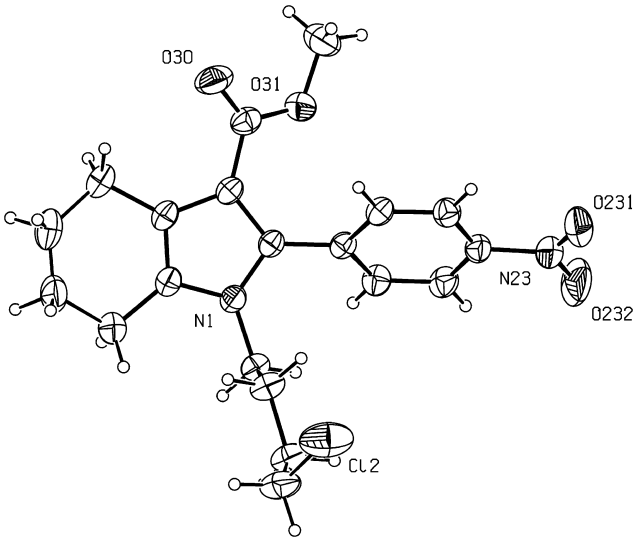
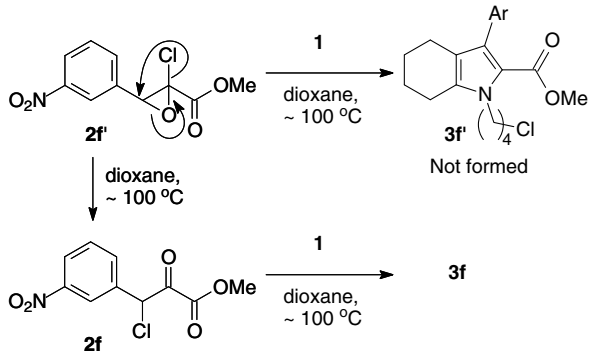


Figure 1. ORTEP drawing of compound **3e**.

with concomitant formation of the new pyrrolidine ring, **D**, and (e) elimination of water leading to formation of tetrahydroindole derivatives **3** (Scheme 2).

The structures of compounds **3a–h** were deduced from their elemental analyses and ^{1}H and ^{13}C NMR data.[16] The mass spectra of these compounds displayed molecular ion peaks at appropriate m/*z* values. Initial fragmentation patterns involved cleavage of the tetrahydroindole ring system.[17] The molecular structure of compound **3e** was confirmed by single-crystal X-ray analysis (Fig. 1).[18]

In addition, it should be pointed out that the reactions of the chloroglycidates (isomeric with chloropyruvates) with enamine **1** proceed in the same way with the formation of tetrahydroindoles **3**. In these cases, the rearrangement of chloroglycidates to isomeric chloropyruvates in boiling dioxane occurs initially[19] (Scheme 3). For example, the reaction of chloroglycidate **2f′** and its isomeric chloropyruvate **2f** with enamine **1** proceeds with formation of the same tetrahydroindole **3f**,[20] which indicated that the rearrangement of chloroglycidate **2f′** to chloropyruvate **2f** proceeds faster than the electrophilic attack of enamine **1** on the C(3) carbon atom of chloroglycidate **2f′** (Schemes 2 and 3). The expected tetrahydroindole derivative **3f′** isomeric to **3f** is not formed.



Scheme 3.

The presented tetrahydroindole synthesis complements other recognized methods and offers significant advantages for the synthesis of indoles with various types of acid sensitive (easily transformable) functional groups. Application of this methodology to the synthesis of tetrahydroindoles using other cyclic enamines and chloroketones is currently under study and the results will be published in due course.

Acknowledgement

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16. Typical procedure for the preparation of **3**. A solution of 1-(1-pyrrolidino)cyclohexene **1** (1.5 g, 10 mmol) and chloropyruvate **2e** (2.6 g, 10 mmol) in dioxane (25 mL) was refluxed for 6 h during which time the colour of the reaction mixture changed from dark green to dark red. The reaction mixture was cooled to ca. 20 °C and a solution of NaOAc (0.27 g, 3.3 mmol) in AcOH (6 mL) was added and the reaction mixture was refluxed for another 2 h and then cooled to ca. 20 °C for 3 h. The reaction solution was evaporated to one-half of the initial volume in vacuo and then washed with 25% aqueous NaCl (4 × 25 mL). The organic extract was dried over $MgSO_4$ and the solvent was removed in vacuo. A crude brown oil was obtained, which after crystallization from *i*-PrOH gave 3.5 g (90%) of an analytically pure sample of 1-chlorobutyl-2-(4-nitrophenyl)-3-methoxycarbonyl-4,5,6,7- tetrahydroindole **3e**: mp 117–119 °C. ^{1}H NMR (600 MHz, DMSO-d_6), δ 1.56–1.66 (4H, m, CH_2CH_2); 1.81–1.88 (2H, m, CH_2); 1.90–1.94 (2H, m, CH_2); 2.60 (2H, t, CH_2, J = 6.1 Hz); 2.79 (2H, t, CH_2, J = 6.1 Hz); 3.38 (2H, t, CH_2, J = 6.1 Hz); 3.62 (3H, s, OCH_3); 3.68 (2H, t, CH_2, J = 7.3 Hz); 7.51 (2H, d, aromatics, J = 7.0 Hz); 8.29 (2H, d, aromatics, J = 7.0 Hz). The tetrahydroindoles **3a**–**d**,**f**–**h** were obtained in the same way using the corresponding α-chloropyruvates.
17. Analytical and other spectroscopic data of tetrahydroindole **3e** (^{13}C NMR, IR, MS) were in good agreement with the proposed structures. MS (EI), m/z (I (%): $M^{+\cdot 37}$Cl 392 (19); 391 (13); $M^{+\cdot 35}$Cl 390 (53); 375(10); 356(32); 355(100); 331(13); 327(10); 313(11); 267(14); 194(10); 91(13); 81(11); 69(16); 55(30); 41(6)).
18. The X-ray diffraction data for the crystal structure of **3e** were collected on a Bruker AXS Kappa Apex diffractometer at 293 K. *Crystallographic data for* **3e**. $C_{20}H_{23}ClN_2O_4$, pink prismatic crystal, formula weight 390.85, monoclinic, $P2_1/c$, a = 9.3894(7), b = 21.7976(15), c = 10.5986(7) Å, β = 114.755(1)°, V = 1969.8(2) Å^3, Z = 4, ρ_{calc} = 1.318 g cm^{-3}, μ (λMoK$_\alpha$ 0.71073 Å) = 0.222 mm^{-1}. F(000) = 824, reflections collected = 16434, unique = 4687, R_{int} = 0.0268, full-matrix least-squares on F^2, parameters = 281, restraints = 14. Final indices R_1 = 0.0567, wR_2 = 0.1573 for 3275 reflections with $I > 2\sigma(I)$; R_1 = 0.0788, wR_2 = 0.1760 for all data, goodness-of-fit on F^2 = 1.040, the largest difference in peak and hole (0.257 and −0.300 e Å^{-3}). Crystallographic data (except structure factors) for structure **3e** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 681280. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
19. Thermal isomerization of methyl 2-chloro-3-(4-nitrophenyl)-2,3-epoxy-propionate[13] **2f** into methyl 3-chloro-3-(4-nitrophenyl)-2-oxopropionate **2f′**. A solution of **2f** (10 mmol) in dioxane (15 mL) was refluxed for 3 h. The solvent was removed in vacuo. The chloropyruvate was obtained as a brown oil, which had satisfactory analytical characteristics, including ^{1}H NMR (600 MHz, DMSO-d_6) spectroscopic data, δ 3.96 (3H, s, OCH_3); 6.22 (1H, s, CH); 7.73 (1H, dd, aromatic, J = 8.5, 8.5 Hz); 7.81 (1H, d, aromatic, J = 8.5 Hz); 8.25 (1H, d, aromatic, J = 8.5 Hz); 8.72 (1H, s, aromatic).
20. Analytical and other spectroscopic data (^{1}H NMR, IR, MS) of tetrahydroindole **3f** obtained from chloropyruvate **2f** and chloroglycidate **2f′** were identical as were the mp's 93.5–95 °C.