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Efficient synthesis of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles based on the synthesis and reactions of (2,4-dioxocyclohex-1-yl)acetic acid derivatives

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Abstract

Acetal-protected (2,4-dioxocyclohex-1-yl)acetic acid derivatives were prepared by the allylation of dilithiated 1,3-cyclohexane-1,3-diones, by the protection of the carbonyl groups and by the oxidation of the alkene. The products were then transformed, by amide formation and subsequent cyclization, into 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles, which represent important intermediates for the synthesis of various alkaloids.

Keywords: Cyclizations; Dianions; N-Heterocycles; Indoles; Oxindoles

2,6-Dioxo-1,2,3,4,5,6-hexahydroindoles represent important key intermediates for the synthesis of various alkaloids including the *Erythrina* and the *Amaryllidaceae* family.[1,2] Haruna and co-workers reported the synthesis of 1-[2-(3-hydroxy-4-methoxyphenyl)ethyl]-3a,4-dihydro-1*H*-indole-2(3*H*),6(5*H*)-dione (based on the Birch reduction) and its transformation into 3-oxoerythrinan.[3] Mariano reported a different strategy based on the aza-Claisen rearrangement of an isoquinuclidine derivative.[4] Recently, Padwa and co-workers reported the synthesis[5] of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles (based on Diels–Alder reactions of 2-imidofurans) and their transformation[6] into spirocyclic alkaloids (e.g., dimethoxyerythratidinone, erysotramidine and *epi*-zephyranthine). Despite their synthetic utility, the scope of these methods is limited to specific examples. Herein, we report what is, to the best of our knowledge, a new strategy for the preparation of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles. Our approach is based on the synthesis of hitherto unknown (2,4-dioxocyclohex-1-yl)acetic acid derivatives, which represent potentially useful building blocks. The straightforward strategy reported herein allows the synthesis of a variety of 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles in good yields.

Our initial attempts to prepare (2,4-dioxocyclohex-1-yl)acetic acid proved to be unsuccessful: the reaction of the dianion[7,8] of cyclohexane-1,3-dione with 1-bromo-2,2-diethoxyethane and epibromohydrin afforded products **2** and **3**, albeit, in low yields (Scheme 1). All attempts to transform **2** and **3** into (2,4-dioxocyclohex-1-yl)acetic acid (**4**) failed. Deslongchamps and Guay recently reported the synthesis of 4-(3-oxopropyl)cyclopentane-1,3-dione by ozonolysis of 4-(but-3-en-1-yl)cyclopentane-1,3-dione.[9] Inspired by this report, we explored a related strategy for the synthesis of acid **4**.

The reaction of the dianion of **1** with allylbromide gave the known[10] product **5** (Scheme 2). Unexpectedly, the ozonolysis of **5** afforded triacid **10** rather than the desired product **11** (Scheme 3). Triacid **10** was also isolated when the oxidation was carried out under different conditions ($KMnO_4$ or $KMnO_4/NaIO_4$ in acetone, $KMnO_4/CuSO_4{\cdot}5H_2O$ in CH_2Cl_2/tBuOH/H_2O). The problem was

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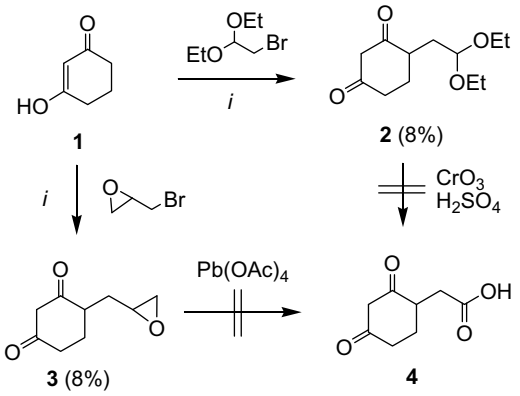
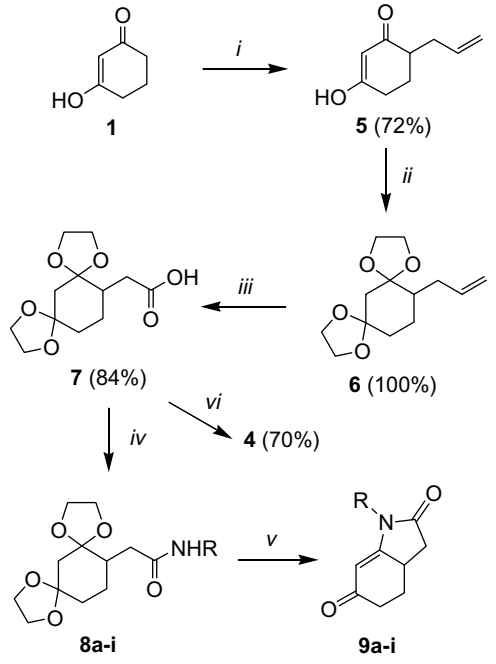
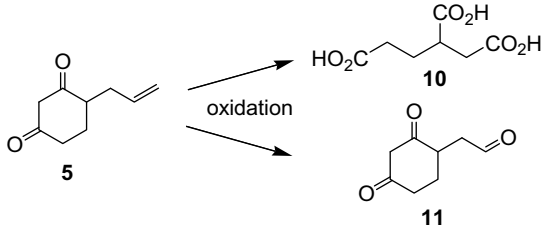


Scheme 1. Attempted synthesis of **4**. Reagents and conditions: (i) (1) 2.5 LDA, HMPTA, THF, −78 °C, 1 h, (2) electrophile, −40→20 °C, 12 h.



Scheme 2. Synthesis of **9a**–**i**. Reagents and conditions: (i) (1) 2.5 LDA, HMPTA, THF, −78 °C, 1 h, (2) allylbromide, −40→20 °C, 12 h; (ii) $HO(CH_2)_2OH$, toluene, *p*-TsOH; (iii) $NaIO_4$, KMO_4, acetone; (iv) (1) DCC, *N*-hydroxysuccinimide, CH_2Cl_2, 1 h, 0 °C, then 12 h, 20 °C, (2) RNH_2, 2 h, 20 °C; (v) PTSA, acetone, 6 h, reflux; (vi) HCl (5%), acetone, reflux, 3 h.



Scheme 3. Oxidation of **5**; conditions: see text.

finally solved by the protection of the carbonyl groups of **5** to give diacetal **6** (Scheme 2). The oxidation of **6** by means of $KMnO_4/NaIO_4$ (in acetone) afforded acid **7**. Although the latter could be transformed into acid **4** in good yield, it proved to be advantageous to directly use diacetal **7** for further transformations. The DCC-mediated reaction of **7** with various primary amines gave amides **8a**–**i** in good yields.[11] Reflux of an acetone solution of **8a**–**i** in the presence of *p*-toluenesulfonic acid (PTSA) afforded the desired 2,6-dioxo-1,2,3,3a,4,5-tetrahydroindoles **9a**–**i** in good yields (Scheme 2, Table 1).[12]

Tetrahydroindole **9j** was prepared from **7** and enantiomerically pure (*R*)-(+)-1-phenylethylamine in 49% overall yield (Fig. 1). The diastereomers could be successfully separated on analytical scale to give the two enantiomerically pure isomers (GC, 30m HP5 column, 190 °C, isotherm, retention times: 49.75 and 51.05 min). Derivative **9k** was prepared from di-medone by the application of the strategy outlined above for the synthesis of **9a**–**i** (Fig. 1).

The structure of all products was established by spectroscopic methods. The structure of **9a** was independently confirmed by X-ray crystal structure analysis (Fig. 2).[13]

In conclusion, we have reported a new synthetic approach to 2,6-dioxo-1,2,3,4,5,6-hexahydroindoles, which represent important key intermediates for the synthesis of various alkaloids. The preparative scope of our strategy and its application to the synthesis of alkaloids is currently being studied.

Table 1
Synthesis of **9a**–**i**

8, **9**	R	% (**8**)[a]	% (**9**)[a]
a	$Ph(CH_2)_2$	64	85
b	$[3,4\text{-}(MeO)_2C_6H_3](CH_2)_2$	65	82
c	Allyl	65	93
d	Ph	70	78
e	Bn	67	86
f	$HO(CH_2)_2$	72	83
g	*c*Hex	65	80
h	*c*Pr	67	62
i	*n*Hept	57	64

[a] Yields of isolated products.

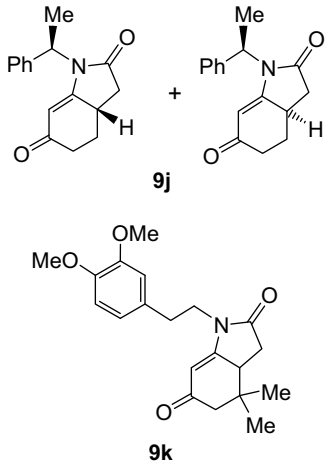


Fig. 1.

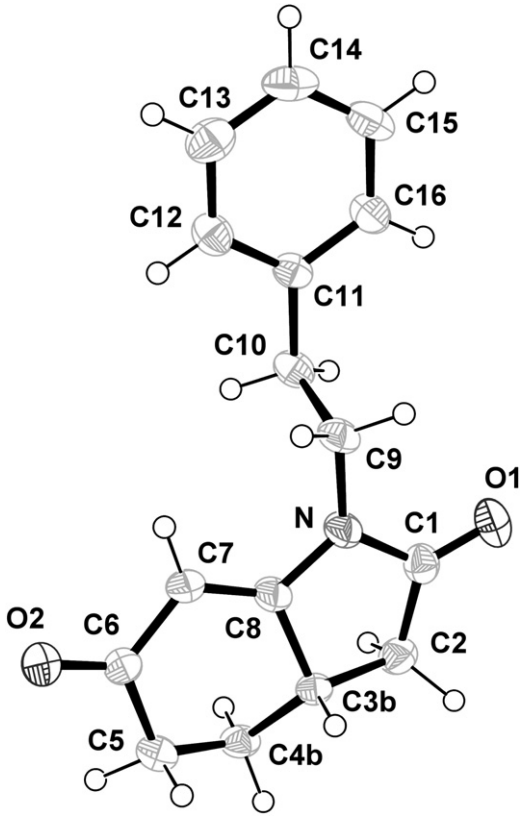


Fig. 2. ORTEP plot of **9a**.

Acknowledgement

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11. *Typical procedure for the synthesis of amides* **8a–f**: To a CH_2Cl_2 solution (20 mL) of **7** (200 mg, 0.77 mmol) were added *N*-hydroxysuccinimide (88 mg, 0.78 mmol) and dicyclohexylcarbodiimide (162 mg, 0.78 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. After stirring for 12 h, the mixture was filtered, 1-amino-2-phenylethane (0.01 mL, 0.85 mmol) was added to the filtrate and the mixture was stirred for 2 h. The mixture was filtered and washed for several times with water (50 mL for each washing). The organic layer was dried ($NaSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptanes–EtOAc) to give **8a** (180 mg, 64%) as a colourless solid.
12. *General procedure for the synthesis of* **9a–f**: An acetone solution of amide **8** and of a catalytic amount of *p*-toluenesulphonic acid was heated under reflux for 6 h. The solution was cooled to 20 °C and concentrated to give a solid residue, which was purified by flash chromatography (silica gel, heptanes–EtOAc) to give compounds **9a–f**. Starting with **8a** (0.58 mmol), PTSA (5 mg, 0.02 mmol) and acetone (15 mL), **9a** was isolated (90 mg, 85%) as a slightly yellow solid, mp = 168 °C. Spectroscopic data of **9a**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.20 (m, 1H, Ar), 7.15 (m, 2H, Ar), 7.10 (m, 2H, Ar), 5.42 (d, $J = 1.7$ Hz, 1H, C=CH), 3.74 (ddd, $J = 13.7$, 8.3, 7.6 Hz, 1H, CH_2), 3.59 (ddd, $J = 13.8$, 8.4, 7.1 Hz, 1H, CH_2), 2.96 (m, 1H, CH), 2.78 (t, $J = 8.1$ Hz, 2H, CH_2), 2.64 (dd, $J = 17.2$, 8.7 Hz, 1H, CH_2), 2.54 (dd, $J = 17.3$, 5.0, 2.0 Hz, 1H, CH_2), 2.34 (dd, $J = 13.4$, 4.9 Hz, 1H, CH_2), 2.19 (m, 1H, CH_2), 2.16 (dd, $J = 17.3$, 8.5 Hz, 1H, CH_2), 1.69 (ddd, $J = 24.8$, 12.2, 4.9 Hz, 1H, CH_2). ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta_C = 196.9$ (C), 175.0 (C), 165.9 (C), 137.2 (C), 128.7 (CH), 128.6 (CH), 126.9 (CH), 101.9 (CH), 41.6 (CH_2), 37.5 (CH_2), 34.8 (CH_2), 34.7 (CH), 32.8 (CH_2), 28.0 (CH_2). IR (KBr, cm^{-1}): $\tilde{\nu} = 3322$ (s), 2931 (m), 1733 (m), 1600 (br). MS (EI, 70 eV): m/z (%) = 255 (M^+, 46), 164 (10), 151 (10), 136 (41), 123 (22), 108 (22), 104 (100), 103 (5), 77 (9). HRMS (EI, 70 eV): calcd for $C_{16}H_{17}O_2N$ [M^+]: $m/z = 255.12538$; found, 255.12593.
13. CCDC 677344 contains all crystallographic details of this publication and are available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk.