Unusual Formation of Tetrahydro-1-isoquinolones from Tetrahydroisoquinoline-1-carboxylic Acids with Carbodiimides and Mechanistic Aspects

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The reaction of tetrahydroisoquinoline-1-carboxylic acids with carbodiimides leads to the formation of tetrahydro-1-isoquinolones in high yields, involving a reaction between mesoionic 1,3-oxazol-5-one intermediates and molecular oxygen.

The importance of carbodiimides as reagents in organic synthesis is well established.[1] Of particular significance is their use as condensing agents in the preparation of amides from carboxylic acids and amines. In the preparation of *N*-methoxyamides from tetrahydroisoquinoline-1-carboxylic acid **1a** and methoxyamine by use of well known carbodiimides such as *N*,*N*′-dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC),† large amounts of 1-isoquinolones **2a** and **3** as by-products were formed.‡ Moreover, the by-product **2a** was formed in a quantitative yield from only **1a** and DCC. The unexpected formation of 1-isoquinolones **2** from tetrahydroisoquinoline-1-carboxylic acids and DCC and mechanistic aspects are reported now.

Table 1 Reactions of carboxylic acids with DCC[a]

Entry	Starting material	Product (% yield)[b]	M.p. or b.p./°C[c] (*p*/mmHg)	^{13}C NMR δ_C (C=O)/ppm
1	**1a**	**2a** (95)	113–114	165.82, 189.15
2	**1b**	**2b** (84)	97–98	165.74, 173.71
3	**1c**	**2c** (80)	210(2)	165.57, 174.42
4	**1d**	**2d** (99)	160(2)	165.78, 189.18
5	**1e**	–	–	–

[a] The reactions were carried out on a 1 mmol scale at 25 °C for 24 h with DCC (1.05 equiv.) in dry CH_2Cl_2 (6 ml). All new compounds reported have been fully characterized by spectroscopic methods and elemental analyses. [b] Isolated yields of pure products. [c] B.p. refers to the bath temperature in a 'Kugelrohr' apparatus.

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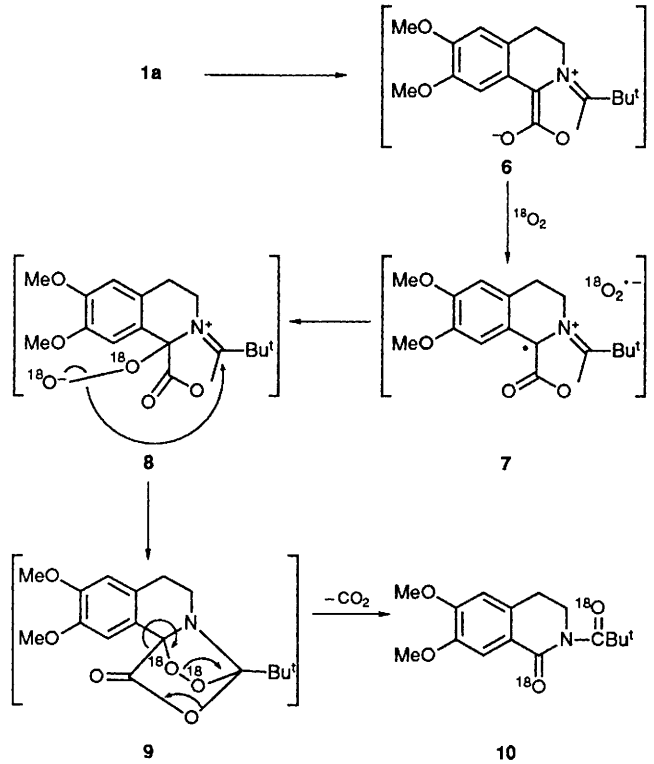
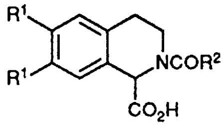
† In general, *N*-methoxyamides are prepared in high yields from the corresponding carboxylic acids and methoxyamine by the carbodiimides condensation.[2]

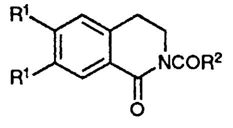
‡ For example, the reaction of **1a** and methoxyamine hydrochloride in the presence of WSC hydrochloride, 1-hydroxybenzotriazole, and triethylamine gave **5a** (17%), **2a** (21%), and **3** (13%). On the other hand, 1,2,3,4-tetrahydroisoquinoline-1-acetic acid **4** afforded the corresponding *N*-methoxyamide **5b** in 92% yield by the same method.



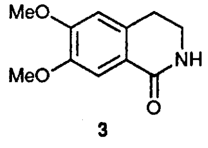
Scheme 1



1 a; R^1 = OMe, R^2 = Bu^t
b; R^1 = H, R^2 = Me
c; R^1 = H, R^2 = Ph
d; R^1 = H, R^2 = Bu^t
e; R^1 = H, R^2 = OEt



2 a; R^1 = OMe, R^2 = Bu^t
b; R^1 = H, R^2 = Me
c; R^1 = H, R^2 = Ph
d; R^1 = H, R^2 = Bu^t
e; R^1 = H, R^2 = OEt



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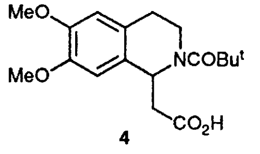

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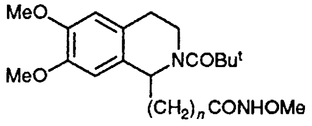

5 a; n = 0
b; n = 1

Variation of the N-substituents, such as N-acyl- and N-ethoxycarbonyl derivatives, was briefly examined. As shown in Table 1, N-acyl derivatives **1a–d** were easily transformed in high yields to the 1-isoquinolones **2a–d**, while N-ethoxycarbonyl derivative **1e** failed to provide **2e**. The imide structure was deduced from spectroscopic data and acid hydrolysis of **2a** gave **3** which was identical with the authentic sample prepared by the literature method.[3] The published preparation of such 1-isoquinolones has required drastic conditions and the yields are generally low (25–50%).[3] This reaction is a new facile synthetic procedure to 1-isoquinolones when the starting materials are easily available.§

An insight into the pathway of the reaction was sought by the detection of CO_2 during the reaction and by conducting the reaction under $^{18}O_2$ atmosphere. Both carbonyl groups of imide in compound **10** contained more than 95% of the ^{18}O label.¶ A tentative mechanism which accounts for the formation of **10** is depicted in Scheme 1. This reaction involves a mesoionic 1,3-oxazol-5-one **6** formed through the cyclodehydration[5] of **1a** by DCC. Intermediate **6** would be the electron donor to O_2. Thus, formation of free radical–superoxide complex **7**, followed by recombination of superoxide with the incipient carbon free radical, might produce hydroperoxide anion **8**.[6] This anion **8** leads to the intermediate **9** which extrudes carbon dioxide to provide the imide **10**. Direct formation of **8** by a concerted interaction between the ground state (singlet) mesoionic compound **6** and ground state (triplet) O_2 is unlikely[6] on the basis of the usual spin conservation rules. For the same reason, formation of **9** by a 1,3-dipolar cycloaddition reaction[7,8] between O_2 and the mesoionic compound **6** may be also unlikely. In spite of the extensive studies of the mesoionic 1,3-oxazol-5-ones,[9] the unusual high ability of molecular oxygen to be incorporated into the mesoionic system has not been reported. This provides the first example of activation reaction of molecular oxygen by the mesoionic 1,3-oxazol-5-ones.

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§ Compounds **1** were prepared by the catalytic hydrogenation of ethyl isoquinoline-1-carboxylate, followed by acylation and subsequent hydrolysis of the resulting ethyl tetrahydroisoquinoline-1-carboxylate.

¶ The ^{13}C NMR spectrum indicated that ^{18}O had been incorporated on both carbonyl groups of imide, based on the observation of ^{18}O-isotope effect[4] on the chemical shifts of both carbonyl carbons. MS and IR data also supported this structure.