Pergamon

Tetrahedron Letters 42 (2001) 3427–3430

TETRAHEDRON LETTERS

An autoxidative approach to 1,2,3,4-tetrahydroisoquinolin-1-one and tetrahydro-β-carbolin-1-one

Michèle Bois-Choussy, Michaël De Paolis and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

Received 22 March 2001; accepted 23 March 2001

Abstract—Treatment of *N*-benzyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate with sodium hydride in *N*,*N*-dimethylformamide gives the corresponding *N*-benzyl 1,2,3,4-tetrahydroisoquinolin-1-one in quantitative yield. The *N*-benzyl 1,2,3,4-tetrahydro-β-carbolin-1-one is prepared in a similar fashion. The *N*-deprotection occurred concomitantly with the oxidative decarboxylation when the nitrogen was benzyloxycarbonylated. © 2001 Elsevier Science Ltd. All rights reserved.

1,2,3,4-Tetrahydroisoquinolin-1-one is a structural unit found in a number of complex natural products such as the *Narcissus* alkaloids narciclasine (**1**) and pancratistatin (**2**) (Fig. 1).[1] It is conventionally prepared by the Bischler–Napieralski reaction from the corresponding *N*-carbamate.[2] However, such conversion usually requires drastic conditions and yields are generally only moderate at best. To overcome this drawback, a modified procedure using a reagent combination (Tf_2O–DMAP) has been developed and applied to the total synthesis of *Amaryllidaceae* alkaloids.[3] Nevertheless, the yield still remains moderate when applied to the synthesis of complex molecules.[4] Alternatively, an intramolecular Friedel–Crafts reaction of isocyanate[5] taking advantage of the facile 6-*exo*-dig mode of cyclization,[6] as well as the condensation of lithiated phthalides,[7] homophthalic anhydrides[8] and lithiated *N*,*N*-diethyl-*ortho*-toluamides[9] with imines[10] followed by ring closure, have been developed for the same purpose. In a series of papers dealing with the chemistry of münchnones, Kawase and co-workers described a synthesis of 1,2,3,4-tetrahydroisoquinolin-1-one by simple treatment of the *N*-acyl tetrahydroisoquinoline-1-carboxylic acid with DCC in dichloromethane.[11] A mechanism involving a formal cycloaddition of oxygen and the münchnone intermediate followed by fragmentation has been advanced. This same transformation (activation of an acid as a mixed anhydride instead of DCC), with a different mechanistic view, has previously been reported from the group of Debaert.[12]

In connection with our ongoing project, we had the occasion to investigate the hydroxymethylation of methyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate (**3**) and found, accidentally, a simple yet high yield synthesis of the title compound (Scheme 1). Thus, treatment of **3a** with sodium hydride (NaH) in *N*,*N*-dimethylformamide (DMF) followed by addition of paraformaldehyde gave, instead of the aldol product, the

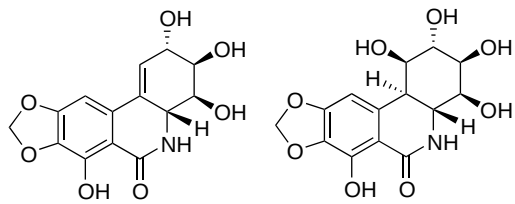
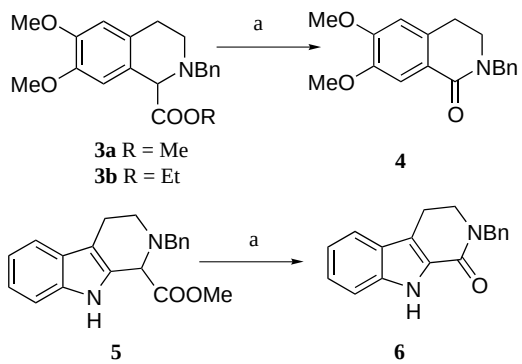


Figure 1.



Scheme 1. (a) NaH, DMF, room temperature.

* Corresponding author. Fax: 33 1 69 07 72 47; e-mail: zhu@icsn.cnrs-gif.fr

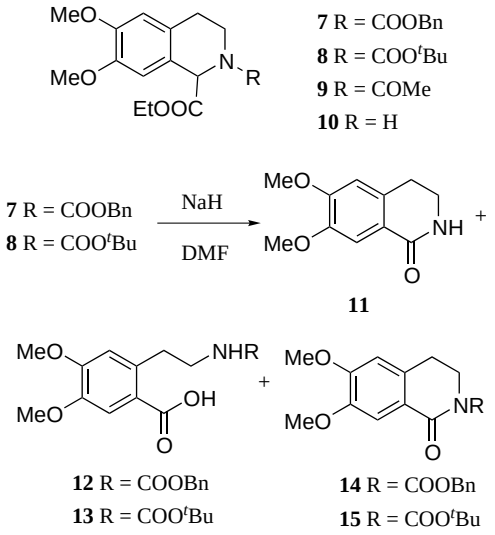
PII: S0040-4039(01)00482-8

corresponding *N*-benzyl tetrahydroisoquinolin-1-one **4** in a quantitative yield. The reaction course was not modified whether the reaction was run at −5°C or at room temperature. Subsequent studies showed that the presence of formaldehyde was not required and that the reaction proceeded smoothly by simply adding a DMF solution of **3a** into the suspension of NaH in the same solvent. The transformation took place readily in dimethyl sulfoxide (DMSO), but not in tetrahydrofurane (THF). The oxidative process dominated even in the presence of a large excess of gaseous formaldehyde. The reaction was accelerated in air-bubbled DMF under an aerobic atmosphere, indicating the role of oxygen in the present process. Nevertheless, the amount of oxygen dissolved in the solvent is sufficient to complete the oxidation. Analytic grade DMF can be used as received from the commercial sources. However, the reaction was slowed down significantly when a freshly redistilled DMF was used. The ethyl ester **3b** was similarly converted to **4** in quantitative yield.

The procedure applied with equal efficiency to the tetrahydro-β-carboline. Thus, treatment of methyl N_b-benzyl-1,2,3,4-tetrahydrocarboline-1-carboxylate (**5**) under identical conditions provided the corresponding N_b-benzyl-1,2,3,4-tetrahydro-β-carbolin-1-one (**6**) in higher than 85% isolated yield. Protection of the indole nitrogen was not required.

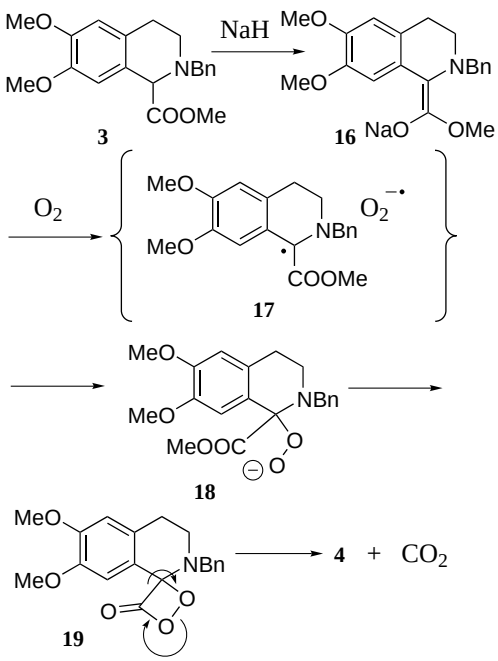
To examine the influence of the *N*-protecting group on the outcome of the reaction, compounds **7**, **8** and **9**, **10** were synthesized. When the *N*-Cbz protected derivative **7** was treated with NaH in DMF, oxidation with concomitant removal of the *N*-benzyloxy carbonyl function occurred to give the tetrahydroisoquinolin-1-one (**11**) and the ring opened amino acid **12** in 80 and 10% isolated yields, respectively. An analytically pure **11** can be obtained by a simple acid–base extraction. Thus, depending on the choice of *N*-protecting group, it is possible to synthesize directly either the *N*-alkylated (**4**) or the *N*-unprotected 1,2,3,4-tetrahydroisoquinolin-1-one (**11**) at will.[13] The reaction of the *N*-Boc derivative **8** produced, under identical conditions, three compounds **11**, **13** and **15** in 10, 50 and 30% yields, respectively.[14] Surprisingly, when the *N*-acetylated derivative (**9**) was subjected to the same reaction conditions, a complex mixture was obtained from which the corresponding tetrahydroisoquinolinone **11** was isolated in less than 10% yield. On the other hand, no oxidation product was isolable from the complex reaction mixture of the *N*-unprotected derivative **10**. Since Kawase's method works only with *N*-acylated tetrahydroisoquinoline-1-carboxylic acid, a different reaction mechanism should thus be envisaged (Scheme 2).

While no detailed mechanistic study was performed, a working hypothesis is depicted in Scheme 3 for the formation of compound **4** from **3**. Enolization followed by single electron transfer (SET) with oxygen gave the stabilized capto-dative radical **17**[15] and the superoxide radical anion that may combine to produce the hydroperoxide anion **18**. Formation of the spiro intermediate **19** followed by fragmentation then afforded the observed compound **4**.[16]

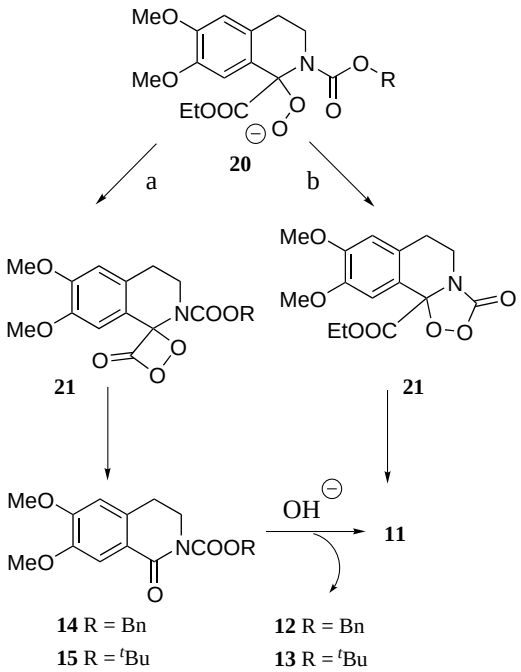


Scheme 2.

The effect of the *N*-protective group on the reaction outcome was intriguing and was indicative of the complex reaction manifolds. The most direct yet logical mechanism that accounts for the results from the reaction of **7** and **8** would involve the formation of imide **14** and **15**, which could then be hydrolyzed to the tetrahydroisoquinolinone **11** and the amino acids **12** and **13** (route a, Scheme 4). In the case of the *N*-Boc tetrahydroisoquinoline **8**, the formation of amino acid **13** as the major product indicated that pathway *a* may be operating. Indeed, when imide **15** (R = O^{t}Bu) was resubmitted to the identical reaction conditions (NaH, DMF, then H_2O), a mixture of the amino acid **13** and



Scheme 3.



Scheme 4.

the tetrahydroisoquinolinone **11** was produced. The preferential formation of the ring opened product from the *N*-Boc lactam is a well-known reaction. Both the steric and the electronic effects should orient predominantly the nucleophilic attack of hydroxide anion onto the *endo* amide carbonyl instead of the *exo* carbamate carbonyl.[17]

The failure to isolate the imide **14** from **7** prompted us to follow the reaction course by ^{1}H NMR using DMSO-d_6 as a solvent. It was observed that the formation of tetrahydroisoquinolin-1-one **11** was accompanied by the concomitant formation of ethanol and benzyl alcohol. The imide intermediate **14** (R = Bn) was undetectable even at the very early stage of the reaction.[18] This observation led us to suppose that an alternative reaction path such as the one involving participation of the *N*-carbamoyl carbonyl function may be operating (Scheme 4, route *b*). The diminished steric hindrance of the *N*-Cbz function may compete favorably with the ester group in intercepting the peroxide anion, leading to the intermediate **21** (Scheme 4). Nevertheless, this mechanistic hypothesis did not allow us to account for the failure of the *N*-acylated derivative **9** to undergo the same oxidative process.

In summary, we have developed an operationally simple yet efficient synthesis of 1,2,3,4-tetrahydroisoquinolin-1-one and 1,2,3,4-tetrahydro-β-carbolin-1-one by an autoxidative process. Since the starting material can be prepared in high yield by the classic Pictet–Spengler reaction,[19] its combination with the present methodology constitutes an attractive alternative to the Bischler–Napieralski reaction for the synthesis of tetrahydroisoquinolinone and should find applications in complex product syntheses.

Acknowledgements

We thank CNRS for financial support. A doctoral fellowship from the MENRT to M.D. is gratefully acknowledged.

References

1. (a) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p. 323; (b) Polt, R. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press, 1996; Vol. 3, p. 109.
2. Sharma, S. D.; Mehra, U.; Gupta, P. K. *Tetrahedron* **1980**, *36*, 3427–3429.
3. (a) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Part 1* **1994**, 3515–3518; (b) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551–2553.
4. (a) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077–3080; (b) Magnus, P.; Sebhat, I. K. *Tetrahedron* **1998**, *54*, 15509–15524; (c) McNulty, J.; Mao, J.; Gibe, R.; Mo, R.; Wolf, S.; Pettit, G. R.; Herald, D. L.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 169–172.
5. (a) Ohta, S.; Kimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2969–2976; (b) Hanessian, S.; Demont, E.; Van Otterlo, W. A. L. *Tetrahedron Lett.* **2000**, *41*, 4999–5003.
6. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
7. Marsden, R.; Maclean, D. B. *Tetrahedron Lett.* **1983**, *24*, 2063–2066.
8. (a) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331–336; (b) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 286–288; (c) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852–2855.
9. (a) Clark, R. D.; Jahangir, *J. Org. Chem.* **1987**, *52*, 5378–5382; (b) Clark, R. D.; Jahangir, *J. Org. Chem.* **1989**, *54*, 1174–1178; (c) Clark, R. D.; Jahangir, Souchet, M.; Kern, J. R. *J. Chem. Soc., Chem. Commun.* **1989**, 930–931.
10. For an asymmetric version based on the chemistry of chiral sulfinimines, see: (a) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627–8634; (b) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901–3903.
11. (a) Kawase, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1328–1329; (b) Kawase, M. *Chem. Pharm. Bull.* **1997**, *45*, 1248–1253.
12. Vaccher, C.; Berthelot, P.; Debaert, M.; Barbry, D. *J. Heterocycl. Chem.* **1984**, *21*, 1201–1204.
13. To a flask containing sodium hydride (15.0 mg, 60% in paraffin, 0.4 mmol) washed twice with pentane was added a solution of ethyl *N*-benzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (**3b**, 71 mg, 0.2 mmol) in DMF (6 mL) at room temperature. After being stirred at the same temperature for 30 min, the reaction mixture was quenched by the addition of an aqueous HCl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and

evaporated to afford analytically pure quinolinone **4** in a quantitative yield. Mp 52–54°C; IR ($CHCl_3$) ν 1638, 1604, 1510, 1480, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.87 (t, $J=6.0$ Hz, 2H), 3.48 (t, $J=6.0$ Hz, 2H), 3.91 (s, 3H), 3.94 (s, 3H), 4.78 (s, 2H), 6.62 (s, 2H), 7.33 (m, 5H), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 27.7, 29.7, 45.7, 50.5, 56.1, 109.4, 110.8, 121.9, 127.4, 128.0, 128.7, 131.8, 137.6, 148.0, 151.9, 164.7; MS (EI) m/z 297. Following the same procedure, the *N*-Cbz derivative **7** was transformed into tetrahydroisoquinolinone **11** in an 80% yield. Mp 171–175°C, lit:[2] 169–171°C; IR ($CHCl_3$) δ 1659, 1606, 1513, 1481, 1339, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.93 (m, 2H), 3.53 (m, 2H), 3.93 (s, 6H), 6.0 (br s, 1H), 6.67 (s, 1H), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 28.2, 40.7, 56.2, 56.3, 109.7, 110.3, 121.5, 132.7, 148.2, 152.2, 166.5; MS (ES) m/z 208 (M+1).

14. More reproducible results were obtained using non-distilled analytically pure DMF. A trace amount of water in DMF seems to be beneficial to the present reaction. Nevertheless treatment of **7** with sodium hydroxide in DMF produced only a trace amount of tetrahydroisoquinolinone.
15. Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148–154.
16. (a) Doering, W. von E.; Haines, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 482–486; (b) Aurich, H. G. *Tetrahedron Lett.* **1964**, 657–658; (c) Bayer, H. O.; Huisgen, R.; Knorr, R.; Schaefer, F. C. *Chem. Ber.* **1970**, *103*, 2581–2597.
17. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.
18. The ^1H NMR spectra of starting material, *N*-alkoxycarbonyl quinolinone and *N*-unprotected quinolinone are easily distinguishable. DMSO-d_6, containing a trace amount of water, was used as received.
19. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.