Novel Oxidation of Substituted Pyrrolidines by *N*-Bromosuccinimide – Rapid Synthesis of Pyrrolo[2,1-*a*]isoquinolines

Judit Tóth,[a] Linda Váradi,[a] András Dancsó,[b] Gábor Blaskó,[b] László Tőke,[a] Miklós Nyerges*[a]

[a] Organic Chemical Technology Research Group of the Hungarian Academy of Sciences, Budapest University of Technology and Economics, P.O.B. 91, 1521 Budapest, Hungary

[b] EGIS Pharmaceuticals Ltd., P.O.B. 100, 1475 Budapest, Hungary
Fax +36(1)4633648; E-mail: mnyerges@mail.bme.hu

Received 11 January 2007

Abstract: A new method for converting 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinolines into 5,6-dihydropyrrolo[2,1-*a*]isoquinolines using *N*-bromosuccinimide as an oxidant is presented.

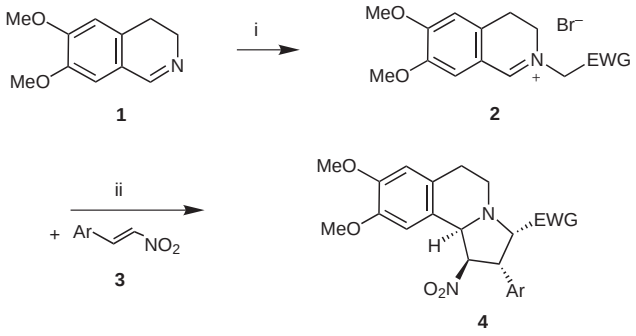
Key words: azomethine ylides, cycloadditions, oxidation, pyrroles

Considerable interest has been shown in substituted pyrrolo[2,1-*a*]isoquinolines due to their diverse biological activities. Since the discovery of the potent cytotoxic and topoisomerase I inhibitor activity of lamellarine alkaloids[1] a number of new synthetic strategies have been developed based on intramolecular oxidative biaryl couplings,[2] thermal reactions of 4-isoxazoline derivatives (obtained by cycloadditions of 3,4-dihydroisoquinoline *N*-oxides with alkynes),[3] intramolecular Heck reactions[4] and cyclizations of 1- or 2-benzylisoquinolines.[5,6]

There are many other methods for the synthesis of pyrrole derivatives, including 1,3-dipolar cycloaddition of azomethine ylides to alkynes followed by aromatization of the intermediate pyrrolines.[7] However, the preparation of pyrroles by dehydrogenation of pyrrolidines has found little application due to the lack of general methods and to the forcing conditions required in most cases.[8]

The development of a method that allows this reaction under mild and neutral conditions should heighten the synthetic potential of this conversion. In this communication we report preliminary results of the direct conversion of one certain type of pyrrolidines into the corresponding pyrroles in excellent yields using *N*-bromosuccinimide (NBS) under mild conditions.

We have decided to study the dehydrogenation of 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinolines **4** which were prepared by 1,3-dipolar cycloadditions of azomethine ylides derived from dihydroisoqinolinium salts previously studied in detail by us.[9] The dipoles produced by dehydrohalogenation reacted with a wide-range of dipolarophiles including maleimides, maleates and nitro olefins. Accordingly, the reaction of **1** with methyl bromoacetate or phenacyl bromides in anhydrous diethyl ether gave the quaternary salts **2**. Reacting these isoquinolinium salts **2** with triethylamine at ambient temperature in the presence of the appropriate dipolarophiles gave the corresponding cycloadducts in high yield (Scheme 1). Alternatively, several of these cycloadducts could be prepared directly from **1** using a one-step method described by us.[9g]



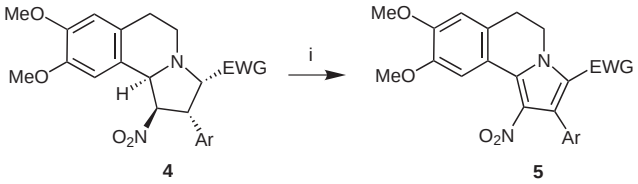
Scheme 1 *Reagents and conditions:* (i) EWG–CH_2Br, Et_2O, r.t.; (ii) Et_3N, EtOH, r.t.

After several unsuccessful exploratory experiments using various oxidizing agents (e.g. MnO_2, DDQ, H_2O_2, $KMnO_4$) we decided to use NBS.[10] NBS is most frequently used in the oxidations of sulfides to sulfoxides[11] and alcohols to carbonyl compounds.[12] This reagent is also useful for the direct transformation of aldehydes into acid bromides[13] or nitriles.[14] However, there are only a few reports on the oxidation of heterocyclic compounds using NBS, these include the oxidation of indoles to isatins,[15] 2,3-dihydrobenzofurans to benzofurans[16] and isoxazoline to isoxazole.[17] There is also a two-step process (halogenation with NBS and then dehydrohalogenation by a base)[18] and in one case a 3,4-dihydroisoquinoline derivative has been aromatized in refluxing carbon tetrachloride in the presence of NBS.[19]

To our delight, we found that the colorless solutions of **4** in chloroform treated with NBS at room temperature turned immediately yellow and after a simple work-up procedure gave the desired 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **5** (Scheme 2).

The reaction is exothermic and on a larger scale, external ice-water cooling is necessary. To demonstrate the generality of this methodology, a broad range of different cycloadducts were chosen. The results are summarized in

SYNLETT 2007, No. 8, pp 1259–1263
Advanced online publication: 08.05.2007
DOI: 10.1055/s-2007-977461; Art ID: D01207ST



4 **5**

Scheme 2 *Reagents and conditions:* (i) NBS, $CHCl_3$, r.t.[20]

Table 1. In general, modest to good overall yields were obtained for all substrates. As a limitation of this method, in the cases when the aromatic ring has two or more electron-donating substituents (Table 1, entries 4, 5 and 12) the concomitant bromination of the 2-aryl substituent was observed during the dehydrogenation process, this could be avoided by using a lower reaction temperature.

Table 1 Oxidation of Substituted Pyrrolidines with NBS

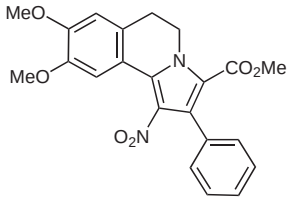
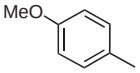
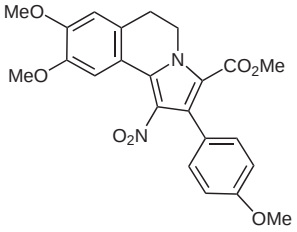
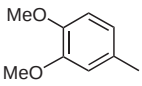
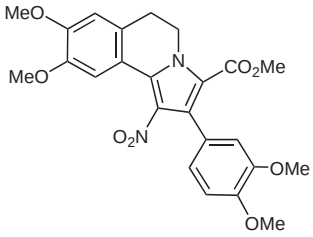
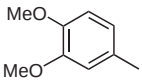
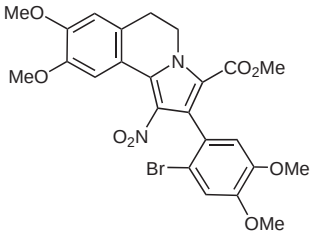
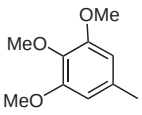
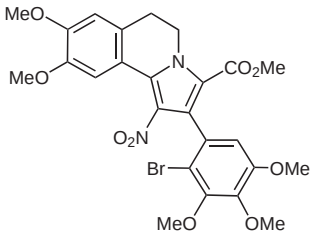
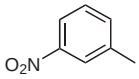
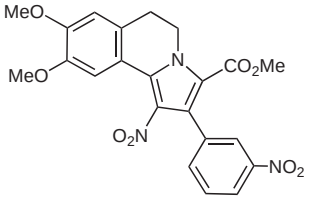
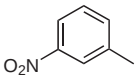
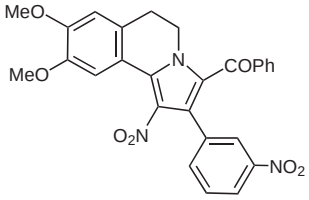
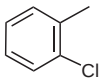
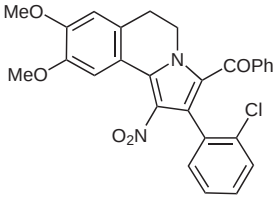
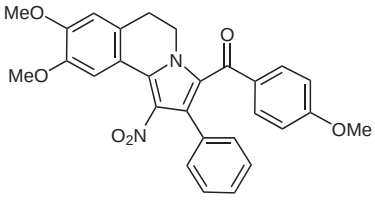
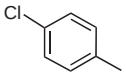
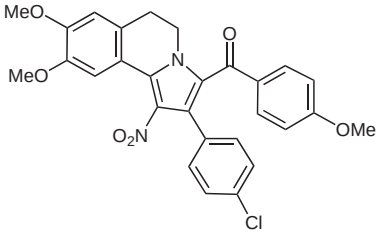
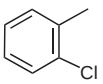
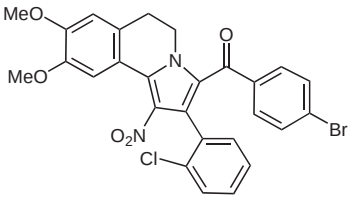
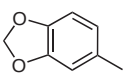
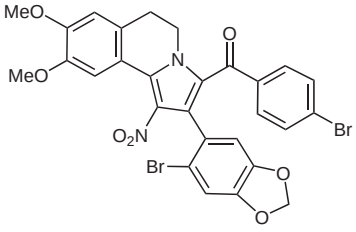
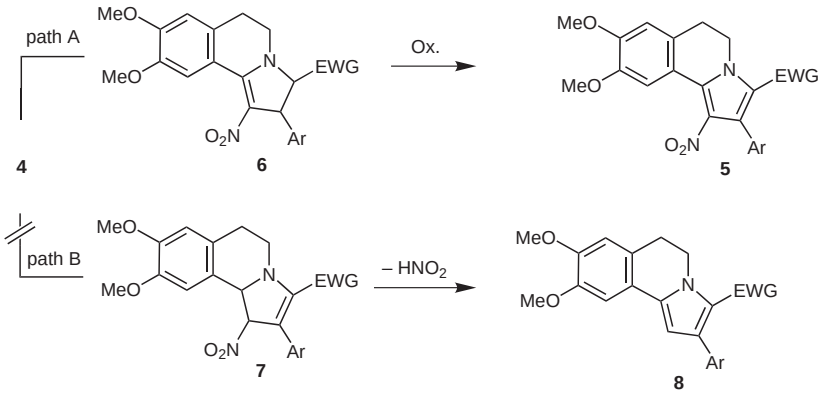
Entry	EWG	Ar	Cycloadduct	Product	Reaction conditions	Yield
1	CO_2Me		**4a**[9g]	 **5a**	r.t.	72%
2	CO_2Me		**4b**[9g]	 **5b**	r.t.	70%
3	CO_2Me		**4c**[9g]	 **5c**	0 °C	81%
4	CO_2Me		**4d**[9g]	 **5d**	0 °C to r.t., NBS (3 equiv)	77%
5	CO_2Me		**4e**[9g]	 **5e**	0 °C, NBS (3 equiv)	60%

Table 1 Oxidation of Substituted Pyrrolidines with NBS (continued)

Entry	EWG	Ar	Cycloadduct	Product	Reaction conditions	Yield
6	CO_2Me		**4f**[9g]	 **5f**	r.t.	81%
7	PhCO		**4g**[9g]	 **5g**	r.t.	85%
8	PhCO		**4h** (69%)	 **5h**	r.t.	58%
9	(4-$MeOC_6H_4$)CO		**4i** (70%)	 **5i**	r.t.	77%
10	(4-$MeOC_6H_4$)CO		**4j** (70%)	 **5j**	r.t.	68%
11	(4-BrC_6H_4)CO		**4k** (73%)	 **5k**	r.t.	5k (59%)
12	(4-BrC_6H_4)CO		**4l** (84%)	 **5l**	0 °C to r.t., NBS (3 equiv)	5l (53%)



Scheme 3

The structures of compounds **5** were determined using NMR spectroscopy (^{1}H, ^{13}C, ^{1}H–^{1}H COSY, ^{1}H–^{1}H NOE and ^{1}H–^{13}C HSQC). The route of the signal and structure assignment of **5e** is shown, as an example in Figure 1.

The mechanism of oxidation of pyrrolidines **4** with NBS has not been clearly established, although based on earlier interpretations, it is generally accepted that a positively charged halogen is the attacking species and gives a brominated intermediate.[10]

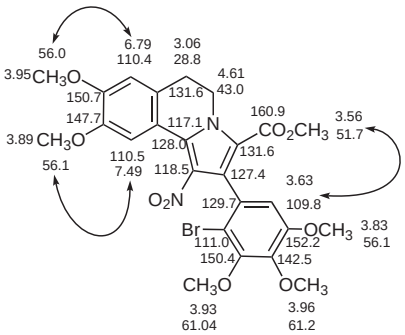


Figure 1

The spontaneous elimination of hydrogen bromide occurs facilitated by the highly conjugated nature of the newly formed double bond. We believe that the pyrrolidines **4** react with NBS to form pyrroline **6** exclusively according to path A. The formation of isomeric pyrroline **7** is unlikely because that would readily lose nitrous acid to form a different pyrrole **8** as product.[21] The last step is a spontaneous dehydrogenation leading to the formation of the isolated pyrroles **5** (Scheme 3).[22]

In summary we have explored a convenient two-step reaction path which provides a useful route to 5,6-dihydropyrrolo[2,1-*a*]isoquinolines **5** via a 1,3-dipolar cycloaddition and an NBS-promoted oxidation sequence. Further studies into oxidizing other heterocyclic compounds using NBS is in progress as well as possible conversions of the formed pyrrole derivatives.

Acknowledgment

This work was financially supported by the *National Fund for Science and Research, Hungary* (OTKA Project No. T 046196). A grant from the *EGIS Pharmaceuticals* provided to J.T. is gratefully appreciated.

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(20) **General procedure for the preparation of compounds 5a–l**: The corresponding cycloadduct (**4**, 1.0 mmol) was dissolved in $CHCl_3$ (10 mL) and NBS (0.17 g, 1.1 mmol) was added in one portion. The solution immediately turned yellow. After 30 min stirring H_2O (10 mL) was added and the organic layer was washed with further portions of H_2O (2 × 10 mL) and brine (10 mL), then dried ($MgSO_4$) and evaporated in vacuo. The residue was triturated with cold EtOH and filtered to yield the title product as a yellow powder. All new compounds afforded correct elemental analyses and spectroscopic data.

Selected examples: Methyl 8,9-dimethoxy-1-nitro-2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**5a**): IR (KBr): 2956, 2833, 1700, 1609, 1591, 1561, 1547, 1506, 1452, 1439, 1355, 1284, 1262, 1236, 1217, 1195, 1181, 1136, 1100, 1072, 1016 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 (m, 4 H, Ph-H and H-10), 7.29 (m, 2 H, Ph-H), 6.79 (s, 1 H, H-7), 4.58 (t, *J* = 6.7 Hz, 2 H, H-5), 3.94 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.06 (t, *J* = 6.7 Hz, 2 H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3 (q), 150.2 (q), 147.9 (q), 136.4 (q), 132.3 (q), 130.9 (q), 129.6 (q), 129.5 (2 × CH), 128.1 (q), 127.8 (CH), 127.6 (2 × CH), 117.2 (q), 114.7 (q), 110.5 (CH), 109.9 (CH), 56.5 (CH_3), 56.0 (CH_3), 51.4 (CH_3), 43.0 (CH_2), 28.8 (CH_2).

Methyl 8,9-dimethoxy-2-(2-bromo-3,4,5-trimethoxyphenyl)-1-nitro-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (**5e**): IR (KBr): 2993, 2940, 2840, 1709, 1669, 1563, 1505, 1475, 1443, 1427, 1410, 1387, 1361, 1343, 1301, 1287, 1260, 1214, 1195, 1138, 1107, 1049, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (s, 1 H, H-10), 6.79 (s, 1 H, H-7), 6.63 (s, 1 H, Ar^2-6′H), 4.61 (m, 2 H, H-5), 3.96 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 3.06 (m, 2 H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.9 (q), 152.2 (q), 150.7 (q), 150.4 (q), 147.7 (q), 142.5 (q), 131.6 (q), 131.5 (q), 129.7 (q), 128.0 (q), 127.4 (q), 118.6 (q), 117.1 (q), 111.0 (q), 110.5 (CH), 110.4 (CH), 109.8 (CH), 61.2 (CH_3), 61.0 (CH_3), 56.13 (CH_3), 56.12 (CH_3), 56.0 (CH_3), 51.7 (CH_3), 43.0 (CH_2), 28.8 (CH_2).

3-(4-Bromobenzoyl)-2-(2-chlorophenyl)-8,9-dimethoxy-1-nitro-5,6-dihydropyrrolo[2,1-*a*]isoquinoline (**5k**): IR (KBr): 3010, 2943, 1633, 1586, 1502, 1471, 1442, 1405, 1355, 1261, 1218, 1148, 1095, 1068, 1056, 1014 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (s, 1 H, H-10), 7.41 (d, *J* = 8.4 Hz, 2 H, Ar^3-2′ and 6′H), 7.25 (d, *J* = 8.4 Hz, 2 H, Ar^3-3′ and 5′H), 7.19 (d, *J* = 7.9 Hz, 1 H, Ar^2-6′H), 7.07 (t, *J* = 7.9 Hz, 1 H, Ar^2-5′H), 6.97 (d, *J* = 7.9 Hz, 1 H, Ar^2-3′H), 6.95 (d, *J* = 7.9 Hz, 1 H, Ar^2-4′H), 6.81 (s, 1 H, H-7), 4.45 (m, 1 H, H-5), 4.34 (m, 1 H, H-5), 3.96 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.10 (m, 2 H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.6 (q), 150.6 (q), 147.8 (q), 136.7 (q), 134.3 (q), 133.1 (q), 132.3 (CH), 132.2 (q), 131.0 (q), 130.9 (2 × CH), 130.5 (2 × CH), 129.3 (CH), 129.1 (CH), 128.3 (q), 127.5 (q), 126.7 (q), 126.3 (CH), 125.3 (q), 117.0 (q), 110.6 (CH), 110.5 (CH), 56.2 (CH_3), 56.0 (CH_3), 43.3 (CH_2), 29.0 (CH_2).

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