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Straightforward synthesis of 11*H*-indolo[3,2-*c*]isoquinoline and benzofuro[3,2-*c*]isoquinoline by ring transformation†

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Abstract—An efficient method was established for the synthesis of 11*H*-indolo[3,2-*c*]isoquinoline and benzofuro[3,2-*c*]isoquinoline using thermal ring transformation of a benzisoxazolo[2,3-*a*]isoquinoline salt.

A series of tetracyclic heteroaromatic compounds based on the indoloquinoline framework have been isolated from *Cryptolepis sanguinolenta*[1] which has been used in traditional medicine in Central and West Africa. More recently one of these alkaloids, cryptosanguinolentine **2b**, was synthetized by us[2] and Molina.[3] Cryptolepis alkaloids and their derivatives possess a number of reported bioactivities, including antibacterial,[4] anti-inflammatory[5] and antiplasmodial[6] activity. These findings as well as some recent reports on the effectiveness of various tetracyclic compounds as anticancer drugs,[7] prompted us to focus our attention in this area. Thus, we report in this paper the synthesis of indolo- and two benzofuro-fused isoquinolines. Thermal cyclization of azidophenyl-quinoline[2] **1** (Fig. 1) was performed in boiling dichlorobenzene and resulted exclusively in the formation of 4-substituted quinoline derivative **2a**, however, when isoquinoline derivative **4** was subjected to the same reaction a new ring system **5** was formed[8] through N–N bond formation, indicating the higher reactivity of the forming nitrene towards the nitrogen atom of the isoquinoline rather than the carbon at position 4. We decided to prepare the isoquinoline analogue **3** of cryptosanguinolentine, which differs

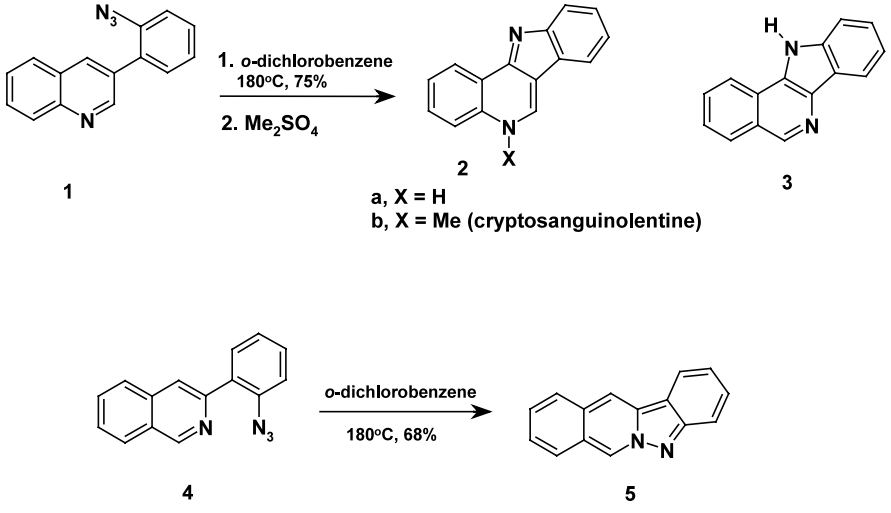

Figure 1.

Keywords: indolo–isoquinoline; benzofuro–isoquinoline; ring transformation; oxenium ion.

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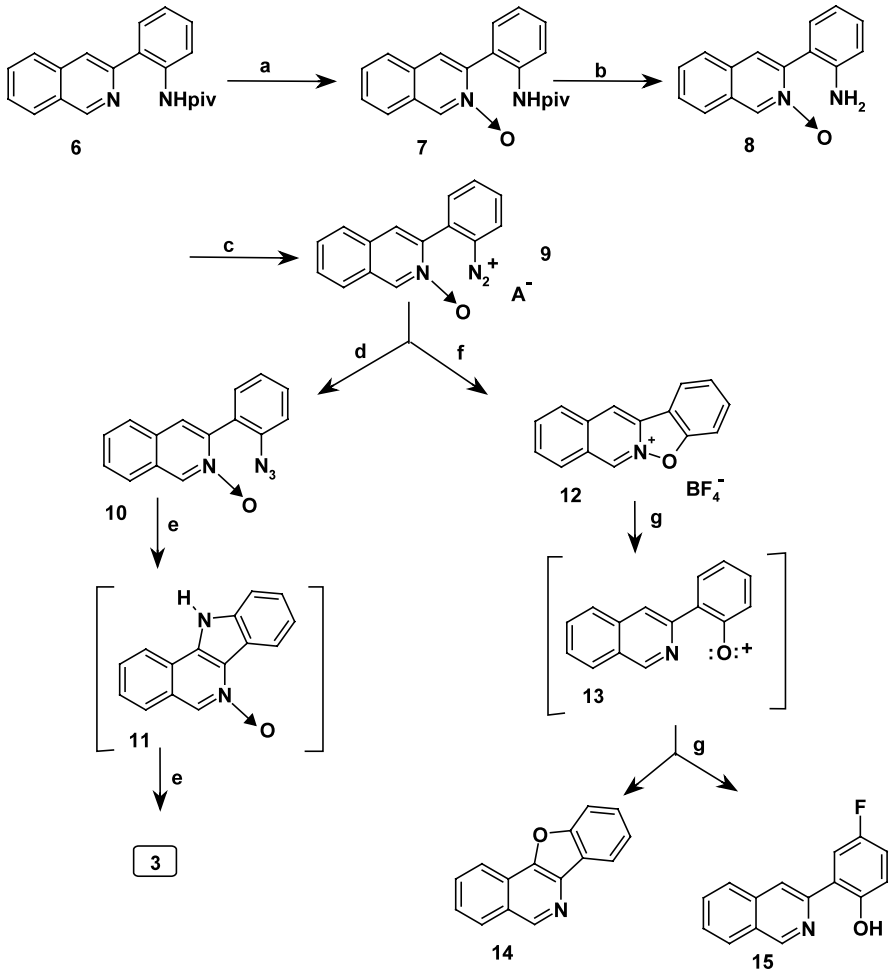
from the natural product only in the position of one nitrogen atom.

In order to block the reactivity of the isoquinoline nitrogen atom in compound **6**, prepared[8] by a Pd-catalysed cross-coupling reaction of 2-(*N*-pivaloylamino)phenylboronic acid and 3-hydroxyisoquinoline-*O*-triflate, in the ring-closure reaction, the *N*-oxide function was introduced **7** using *m*CPBA. It was expected that this would be an easily removable protecting group, which would not influence the reactivity of the isoquinoline ring at position 4 (Scheme 1). After hydrolysis, the amino-compound **8** was transformed to the corresponding azide **10** via diazotisation followed by reaction with sodium azide. However, besides the azido compound **10** a new product, benzisoxazolo[2,3-*b*]isoquinoline salt **12** was also isolated, the details of which are discussed later. It was anticipated that the methodology successfully used previously[9] for the synthesis of polyfused heterocycles could be employed for the thermal cyclisation of azide **10**, however, the expected *N*-oxide derivative **11** was not formed. Instead, the desired final product, tetracyclic 11*H*-indolo[3,2-*c*]isoquinoline[10] **3** was isolated in moderate yield. This reaction can be interpreted by cyclisation of the azido-compound through formation of an intermediate nitrene followed by thermal deoxygenation of the ring-closed product **11**. This assumption seemed to be supported by our earlier finding[8] that thermal cyclisation of the deoxy derivative of **10** (i.e. **4**) gave exclusively **5** and formation of **3** was not detected.

Formation of the new ring-system, benzisoxazolo[2,3-*b*]isoquinoline **12** can be interpreted by a nucleophilic attack of the *N*-oxide at the electrophilic carbon atom bearing diazonium group, followed by nitrogen elimination. A similar reaction was earlier observed by Abramovitch[11] and most recently it has been proved that tertiary propargylamine *N*-oxides easily undergo a new type of rearrangement[12] through formation of an isoxazoline intermediate. Compound **12** was obtained in a higher yield when the diazonium salt was used in the stable tetrafluoroborate form prepared by adding a cold aqueous ammonium tetrafluoroborate solution to the diazotized mixture. It is known from the literature,[13] that the generation of aryloxenium ions has been proposed in the thermolysis of the benzisoxazolo[2,3-



Scheme 1. *Reagents and conditions*: (a) *m*CPBA, $CHCl_3$, r.t., 1 d, 76%; (b) 20% H_2SO_4, reflux, 7 h, 92%; (c) conc. HCl, $NaNO_2$, 0°C, 1 h, then $NH_4^+BF_4^-$, 0°C, 1 h, 65%; (d) NaN_3, 0°C, 1 h, 63%; (e) *o*-dichlorobenzene, 150°C, 6 h, 43%; (f) CH_3CN, r.t., 8 h, 82%; (g) *o*-dichlorobenzene, MW, 170°C, 30 min, 65% (**14**), 13% (**15**).

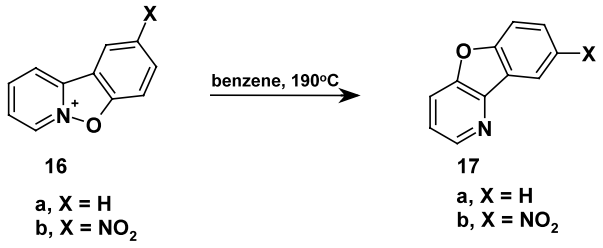


Figure 2.

a]pyridinium **16** ring system (debenzologue of **12**). It was hoped that the generation of the aryloxenium ion from this salt would lead to intramolecular substitution of the pyridine ring.

Thermolysis of **16a** failed to yield benzofuro[3,2-*b*]pyridine **17a**. It was reasoned that this could be due to the proposed oxenium ion intermediate not being electrophilic enough to attack a pyridine β-position. Introduction of a nitro group *para* to the oxygen atom should remedy this problem. Indeed, thermolysis of **16b** gave **17b** in 20% yield (Fig. 2). The fact that oxenium ions are isoelectronic with nitrenes adds another dimension to the interest in these species. Because of the high reactivity at C-4 of the isoquinoline ring towards electrophiles,[14] an increase in the amount of ring transformation product **14** compared to **17** would be expected without activation of aryloxenium ion by the nitro group. Indeed, when linearly fused isoxazolium salt **12** was heated in *o*-dichlorobenzene facile ring transformation took place to give the expected benzofuro[3,2-*c*]isoquinoline[15] **14** together with a little of the *para*-fluorophenol derivative **15**, the formation of which can be interpreted by a nucleophilic attack of fluoride at the *para* position of the phenyloxenium cation **13** similar to the Schiemann reaction.[16] This consideration was supported by replacing the BF_4^- anion of **12** with HSO_4^-; in this case the formation of phenol derivative **15** was not detected.

In summary, we have elaborated a concise synthesis of two closely related isomers (**3** and **14**) of natural cryptosanguinolentine **2b**. This route seems to provide a general method for the preparation of various substituted derivatives of *c*-fused indolo- and benzofuro-isoquinolines using appropriately substituted isoquinolines and substituted *N*-pivaloylamino arylboronic acids and opens the way for their biological evaluation.

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15. Selected data for compounds in Scheme 1: (a) Data for **9**: BF_4^- salt, ^{1}H NMR (CD_3CN) δ 9.05 (1H, s), 8.61 (1H, d, $J=8$ Hz), 8.4 (1H, s), 8.38 (1H, m), 8.12–7.94 (4H, m), 7.84–7.26 (2H, m). IR (KBr) $\nu=3102$, 2284, 1561, 1310, 1060, 770 cm^{-1}; (b) Data for **10**: ^{1}H NMR ($CDCl_3$) δ 8.86 (1H, s), 7.79 (1H, d, $J=8$ Hz), 7.74 (1H, d, $J=8$ Hz), 7.70 (1H, s), 7.62–7.58 (2H, m), 7.53 (1H, m), 7.45 (1H, d, $J=7.5$ Hz), 7.30 (1H, d, $J=7.5$ Hz), 7.27 (1H, m). IR (KBr) $\nu=2086$, 1435, 1315, 1285, 1127, 760 cm^{-1}; (c) Data for **3**: ^{1}H NMR (DMSO-d_6) δ 12.3 (1H, s), 9.12 (1H, s), 8.51 (1H, d, $J=7.7$ Hz), 8.29 (1H, d, $J=8$ Hz), 8.24 (1H, d, $J=8$Hz), 7.91 (1H, m), 7.70 (1H, m), 7.69 (1H, d, $J=7.6$ Hz), 7.49 (1H, m), 7.31 (1H, m), ^{13}C (DMSO-d_6) δ 144.5, 138.4, 133.4, 129.8, 128.4, 127.2, 126.4, 126.1, 125.4, 123.4, 122.6, 121.1, 119.7, 119.1, 111.7 ppm; (d) Data for **12**: ^{1}H NMR (CD_3CN) δ 10.31 (1H, s), 9.22 (1H, s), 8.52 (1H, d, $J=8$ Hz), 8.45–8.44 (2H, m), 8.23 (1H, m), 8.10 (1H, m), 8.01 (1H, m), 7.90 (1H, d, $J=8.0$ Hz), 7.79 (1H, m). ^{13}C (CD_3CN) δ 156.2,

137.5, 136.9, 135.3, 134.6, 132.6, 130.1, 128.9, 128.1, 126.3, 123.9, 120.1, 118.3, 118.1, 110.3 ppm. IR (KBr) $v=1643$, 1460, 1371, 1225, 1084, 1058, 769 cm^{-1}; (e) Data for **14**: ^1H NMR (DMSO-d_6) δ 9.38 (1H, s), 8.41 (1H, d, $J=7.7$ Hz), 8.39 (1H, d, $J=7.7$ Hz), 8.22 (1H, d, $J=8.0$ Hz), 8.0 (1H, m), 7.91 (1H, d, $J=8.0$ Hz), 7.82 (1H, m), 7.64 (1H, m), 7.54 (1H, m); (f) 21Data for **15**: ^1H NMR (DMSO-d_6) δ 9.82 (1H, s), 9.18 (1H, s), 8.54 (1H, d, $J=8.0$ Hz), 8.18 (1H, d, $J=8.0$ Hz), 8.10 (1H, m), 8.09 (1H, d, $J=10$ Hz), 7.90 (1H, m), 7.30 (1H, dd, $J=12$Hz, 9 Hz), 7.07 (1H, dd, $J=5$ Hz, 9 Hz).

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