C. R. Chimie 18 (2015) 127–131

Contents lists available at ScienceDirect

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Preliminary communication/Communication

Differential nitrogen–carbon bond cleavages in architecturally complex molecular scaffolds containing a bridge-head nitrogen atom

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ARTICLE INFO

Article history:
Received 8 April 2014
Accepted after revision 18 April 2014
Available online 13 January 2015

Keywords:
Heterocyclic
Benzazepine
Tetrahydroprotoberberine
Steric
Electronic

ABSTRACT

Application of an N–C bond cleavage reaction in various structurally complex molecular frameworks containing bridge-head nitrogen atom offered differential outcomes that were attempted to rationalize invoking both steric and electronic factors.

1. Introduction

During a synthetic program aimed at generating biologically active novel neurological agents, we sought to carry out synthetic transformations from structurally complex bridge-head heterocyclic indoline fused benzazepine class of compound **1** to compound **2** (Fig. 1).

Our anticipation was based on a literature reported similar N–C_8 bond cleavage reaction. For example, refluxing biologically active natural product tetrahydroprotoberberine class of compounds **3** in ethyl chloroformate generated compound **4** (method *a*, Fig. 2; note the numbering systems in compounds **1** and **3** and afterwards maintain the same pattern for the uniformity in the discussion) [1–4]. A modified procedure of treating compound **3** in acetone with ethyl chloroformate in the presence of sodium iodide at room temperature and in dark to generate compound **5** (method *b*, Fig. 2) had been also reported [5,6].

2. Chemistry

Compound **1** was accessed by following a literature reported procedure [7]. Once in hand, refluxing the compound **1** with excess ethyl chloroformate over a period of 24 h resulted in no appreciable change of the starting material. On the other hand, treatment of compound **1** in acetone with ethyl chloroformate in the presence of sodium iodide resulted in exclusive cleavage, not at expected C_8–N bond but at C_6–N bond generating compound **6**, instead of the anticipated compound **2** (Scheme 1).

The mode of cleavage was proven by reduction of compound **6**, with lithium aluminum hydride, to the corresponding tertiary base **7**. The ^{1}H NMR spectrum of compound **7** displayed a three-proton triplet at δ 1.14 with a coupling constant of 7.5 Hz and a two-proton quartet at δ 2.57 with a coupling constant of 7.5 Hz representing the aromatic $-CH_2CH_3$ group. The spectrum also exhibited three-proton singlet at δ 2.49 for the N–CH_3 group.

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http://dx.doi.org/10.1016/j.crci.2014.04.006
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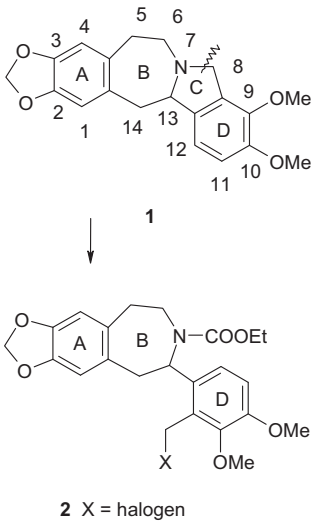


Fig. 1. Anticipated transformations from compound **1** to compound **2**.

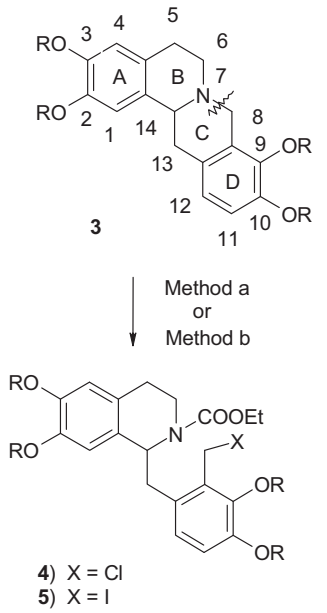
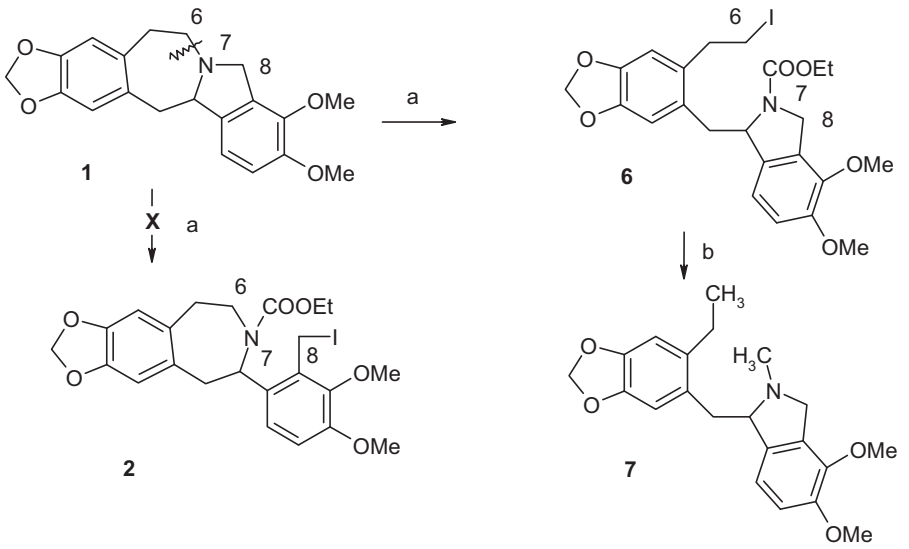


Fig. 2. Reported ring fragmentation procedures.

Concurrently, we were also developing a total synthesis of the novel tetrahydrohomoprotoberberine compound **8** (Scheme 2). Commercially available compound **9** was converted to compound **10** [5]. Compound **10**, on treatment with sodium cyanide, produced compound **11** that underwent basic hydrolysis (sodium hydroxide) to generate compound **12** without affecting the *N*-ethoxycarbonyl group. Its removal needed a harsher condition with careful monitoring by heating compound **12** at a high temperature in a sealed tube in the presence of potassium hydroxide to generate compound **13**. Subsequent internal cyclization of the amino acid **13** to lactam **14** was carried out in hot decalin. Compound **14** was reduced by lithium aluminum hydride to generate the free base **8**.

The difference in behavior of compounds **1** and **3** in the bond cleavage reactions as well as the availability of compound **8** at this stage prompted us to explore its behavior in the same paradigm. Treatment of compound **8** in refluxing ethyl chloroformate [Scheme 3, step (a) (i)] overnight resulted in the production of a compound (50% yield), displaying a deep blue fluorescence under short UV light. The same product was also generated in 90% yield when Rönsch protocol [Scheme 3, step (a) (ii)] was followed. The ^{1}H NMR spectrum of the compound revealed two one-proton doublets at δ 6.81 and δ 6.85, respectively, with a coupling constant of 13.5 Hz, indicating two vicinal protons of an olefinic moiety of



Scheme 1. Reagents and conditions. (a) Ethyl chloroformate, NaI, acetone, dark, room temperature, 72 h, 70%; (b) LAH, ether, heat, 1 h, 65%.