Tetrahedron 65 (2009) 6050–6056

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# A rapid and efficient entry to synthesis of quino and chromenocarbazoles via Ullmann–Goldberg condensation

Ramu Meesala, Rajagopal Nagarajan *

*School of Chemistry, University of Hyderabad, Central University (P.O.), Hyderabad-500 046, India*

ARTICLE INFO

*Article history:*
Received 27 January 2009
Received in revised form 11 May 2009
Accepted 22 May 2009
Available online 28 May 2009

ABSTRACT

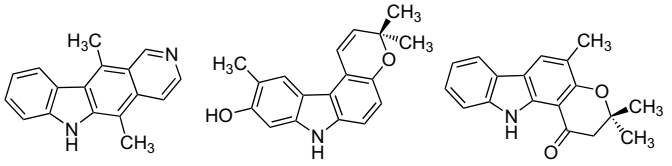
An efficient two-step method for the preparation of quino and chromenocarbazoles via Ullmann–Goldberg condensation of 3-aminocarbazole and 3-hydroxy-9-ethylcarbazole with *o*-halobenzoic acids followed by cyclization with $POCl_3$ has been described.



## 1. Introduction

Aryl and heteroarylcarbazoles are important classes of biologically active compounds that include notable alkaloids of pharmaceutical interest[1] are heteroaryl annulated derivatives of carbazole. It is well established that the pyridocarbazole ring system is an appropriate skeleton to design DNA intercalating drugs.[2] For example, ellipticine[3] and its natural analogues have received a vast amount of attention because of their anticancer properties due to the interaction with DNA. Pyranocarbazole alkaloids[4] such as glycoborinine and euchrestifoline are an important class of compounds and glycoborinine, isolated from *Glycosmis arborea*, applied against fever, liver complaints, and certain other diseases.[5]

As a result of their significant potential as therapeutics, interest has grown in the development of methods for the efficient and rapid synthesis of the derivatives of pyrido and pyranocarbazoles especially because the current methods, which involve multi-step reactions, lower yields, longer reaction times, and high cost of palladium,[1b,3b,i,k] are unsatisfactory. Herein, therefore, we described a simple, economical, and effective two-step procedure for the synthesis of quino and chromenocarbazoles based on C–N and C–O bond formation through Ullmann–Goldberg condensation[6] followed by intramolecular Friedel–Crafts[7] cyclization with $POCl_3$. Since the starting materials *o*-halobenzoic acids can be readily prepared by diazotization of anthranilic acid[8] derivatives and the reagents CuI and $POCl_3$ are relatively cheap, our synthetic methodology for the preparation of quino and chromenocarbazoles is simple and efficient.



Ellipticine Glycoborinine Euchrestifoline

## 2. Results and discussion

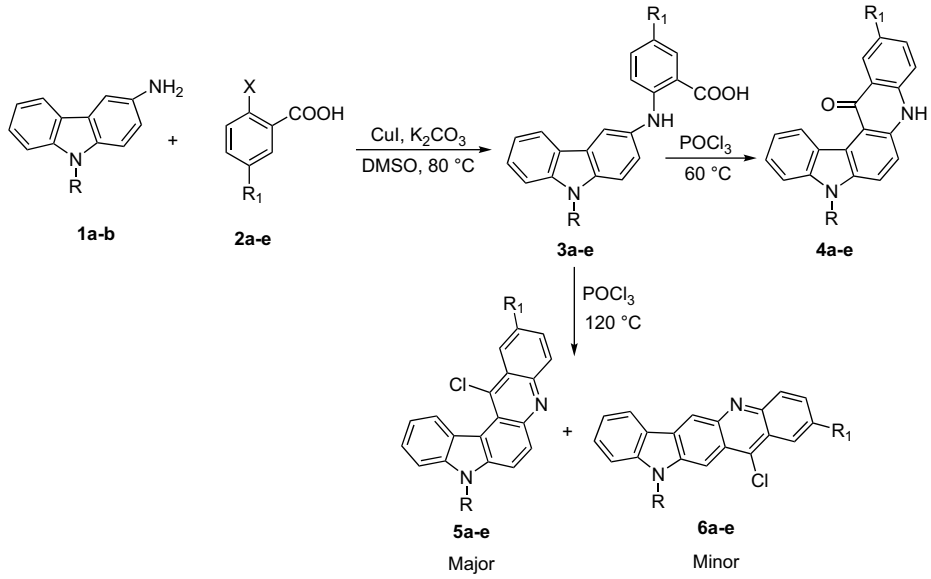
As shown in Scheme 1, we have carried out the condensation of 3-amino-9-ethylcarbazole **1** with various *o*-iodobenzoic acids **2a–e** in presence of CuI (0.1 equiv) and $K_2CO_3$ (2.0 equiv) without any ligand in DMSO at 80 °C. The reaction also works with 3-aminocarbazole and the corresponding product **3a** is obtained in 71% yield. Facile reaction without any ligand is due to the activation of halogens with the *ortho* carboxylic group.[9] In the absence of CuI, no condensation was observed. Outcome of the condensations is presented in Table 1. The structure of **3b** was also confirmed by the single crystal X-ray analysis[10] and Figure 1 shows the ORTEP diagram of **3b**. Due to the activation of the strong electron-withdrawing nitro group, the time required for the formation of **3e** was comparatively reduced to half of the other iodobenzoic acids. Since the order for ease of halogen displacement follows as I>Br>Cl, 2-bromobenzoic acid has required longer reaction time.

Interestingly, diazocarbazole was obtained as a by product (<5%) during the coupling between 3-amino-9-ethylcarbazole and *o*-halobenzoic acids. The structure of diazocarbazole was also confirmed by single crystal X-ray analysis.[10] The aerobic oxidation of CuI produces the active Cu(II) species, which oxidizes the aminocarbazole to the corresponding diazocarbazole.[11]

The products **3a–e** were subjected to cyclization with $POCl_3$ as shown in Scheme 1. At 60 °C, **3a** undergoes facile cyclization to give

* Corresponding author. Tel.: +91 040 66794831; fax: +91 040 23012460.
*E-mail address:* rnsc@uohyd.ernet.in (R. Nagarajan).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.061




**Scheme 1.** Synthesis of quinocarbazoles.

**Table 1**
Synthesis of quinocarbazoles

| S. no. | R | $R_1$ | X | Condensed product | Time (h) | Yield (%) | Cyclized product | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | I | **3a** | 1 | 73 | **4a** | 1 | 71 |
| | | | | | | | **5a** | 1 | 73 |
| | | | | | | | **6a** | 1 | 10 |
| 2 | Et | H | I | **3b** | 1 | 73 | **4b** | 1 | 76 |
| | | | | | | | **5b** | 1 | 78 |
| | | | | | | | **6b** | 1 | 12 |
| 3 | Et | Cl | I | **3c** | 1 | 72 | **4c** | 1 | 73 |
| | | | | | | | **5c** | 1 | 74 |
| | | | | | | | **6c** | 1 | 14 |
| 4 | Et | Br | I | **3d** | 1 | 70 | **4d** | 1 | 72 |
| | | | | | | | **5d** | 1 | 75 |
| | | | | | | | **6d** | 1 | 13 |
| 5 | Et | $NO_2$ | I | **3e** | 0.5 | 74 | **4e** | 1 | 75 |
| | | | | | | | **5e** | 1 | 75 |
| | | | | | | | **6e** | 1 | 12 |
| 6 | Et | H | Br | **3a** | 3 | 64 | **4a** | 1 | 76 |
| | | | | | | | **5a** | 1 | 78 |
| | | | | | | | **6a** | 1 | 12 |

the corresponding product **4a** in good yield. The reaction works well for other substituted *o*-halobenzoic acids (Scheme 1 and Table 1). The structure of **4c** was also confirmed by the single crystal X-ray analysis[10] (see Fig. 2). When the reaction was performed at 120 °C, two regioisomeric quinocarbazoles were formed. Compounds **5a**–**e** were formed as a major products along with minor

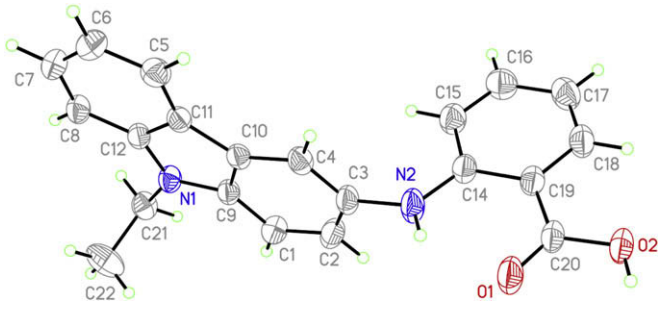



**Figure 1.** ORTEP diagram of **3b**.

products **6a**–**e** (Scheme 1). These two isomers have been identified from $^1$H NMR spectrum. The presence of two singlets at $\delta$ 8.85 and 7.96 ppm differentiate the regioisomer **6c** from the other regioisomer **5c** in which two doublets are present in the same region. The structures of these two isomers were also confirmed by the single crystal X-ray analysis[10] (see Fig. 2).

The same method was successfully extended to 3-hydroxy-9-ethylcarbazole. 3-Hydroxy-9-ethylcarbazole **7** condensed with *o*-halobenzoic acids to provide the corresponding products **8a**–**d** in good yield and the results were summarized in Table 2. As shown in Scheme 2, the condensed products **8a**–**d** underwent cyclization to the corresponding chromenocarbazoles after treating with excess of $POCl_3$. In this case, only one regioisomer **9a**–**d** was formed at 60 °C. The structure of **9a** was also confirmed by single crystal X-ray analysis[10] as shown in Figure 3.

## 3. Conclusion

In conclusion, we have developed a new, fast, and efficient route to the synthesis of quino and chromenocarbazoles via Ullmann–Goldberg condensation followed by intramolecular Friedel–Crafts cyclization with $POCl_3$.

## 4. Experimental

### 4.1. General

The procedure does not require inert atmosphere. All the products obtained were purified by column chromatography using silica gel (100–200 mesh). Hexane was used as a co-eluent. $^1$H and $^{13}$C NMR were recorded in Brucker 400 and 100 MHz spectrometers, respectively. The chemical shifts are reported in parts per million downfield to TMS ($\delta$=0) for $^1$H NMR and relative to the central $CDCl_3$ resonance ($\delta$=77.0) for $^{13}$C NMR. We have observed that the compounds **5a**– and **6a**– were converting to their corresponding keto compounds **4a**– in DMSO-$d_6$. This may be due to the presence of moisture in DMSO-$d_6$. So, later we have recorded $^1$H and $^{13}$C NMR of the compounds **4a**–**e** and **6a**– in $CDCl_3$. LC–MS was used for the mass spectral analysis. IR spectra were recorded on a FT-IR spectrometer using KBr pellets. Elemental analysis was carried out in CHN analyzer EA 1112, Thermo Finnigan. Elemental