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Efficient Syntheses of the Unknown Quinolino[2,3-*c*]cinnolines; Synthesis of Neocryptolepines

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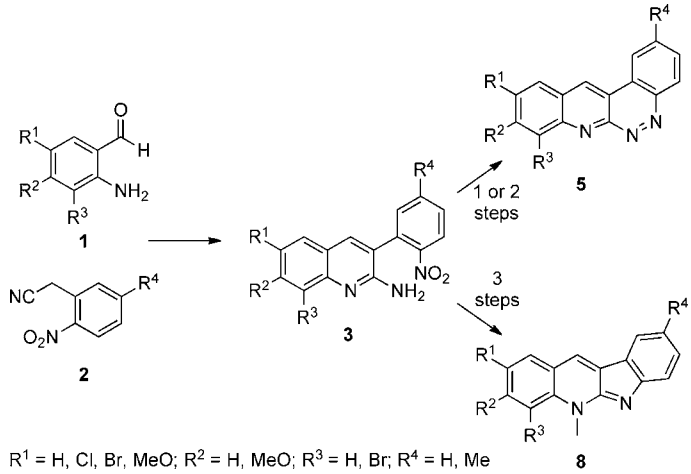
ABSTRACT



A facile, efficient, three-step protocol for the synthesis of the unknown quinolino[2,3-*c*]cinnoline 5 is introduced. In addition, a new approach for the preparation of the biologically active neocryptolepines 8 in good overall yields is described.

Quinolines and their heterofused derivatives represent an interesting class of nitrogen-containing heterocycles that have gained attention due to their broad biological activities including antimalarial, antiparasitic, antifungal, antibacterial, cytotoxic, anti-inflammatory, and antihyperglycemic.[1] Although numerous elegant methods have been developed for the synthesis of heterofused quinoline derivatives,[2] none of them describes the synthesis of the unknown quinolino[2,3-*c*]cinnoline **5**. We now introduce a facile, highly efficient, three-step protocol for the synthesis of **5** by employing an extension of the Friedländer reaction,[2d] which involves condenstation of *o*-aminobenzaldehydes **1a**−**d** with *o*-nitroaryl acetonitriles **2a**,**b** to afford a number of novel 2-amino-3-(2-nitroaryl)quinolines **3** (Table 1). In addition to providing access to quinolino[2,3-*c*]cinnolines (**5**), 2-amino-3-(2-nitroaryl)quinolines **3** have also been utilized for a new and efficient synthesis of the naturally occurring

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(1) (a) Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010**, *17*, 2348. (b) Kakadiya, R.; Dong, H.; Kumar, A.; Narsinh, D.; Zhang, X.; Chou, T.; Lee, T.; Shah, A.; Su, T. *Bioorg. Med. Chem.* **2010**, *18*, 2285. (c) Deb, I.; Paira, P.; Hazra, A.; Banerjee, S.; Dutta, P.; Mondal, N.; Das, S. *Bioorg. Med. Chem.* **2009**, *17*, 5782. (d) Upadhayaya, R.; Kulkarni, G.; Vasireddy, N.; Vandavasi, J.; Dixit, S.; Sharma, V.; Chattopadhyaya, J. *Bioorg. Med. Chem.* **2009**, *17*, 4681. (e) Balasubramanian, M.; Keay, J. G. I. Pergamon Press: Oxford, 1996; Vol. 5, p 245.

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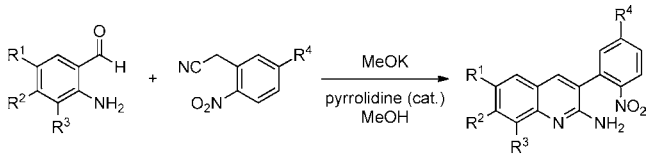
Table 1. Synthesis of 2-Amino-3-(2-nitroaryl)quinolines **3**



1 2 3

1	R^1	R^2	R^3	2	R^4	3	mp (°C)	yield (%)
a	H	H	H	**a**	H	**a**	205−207	73
a	H	H	H	**b**	Me	**b**	201−203	71
b	Cl	H	H	**a**	H	**c**	255−257	70
c	Br	H	Br	**a**	H	**d**	142−144	62
d	MeO	MeO	H	**a**	H	**e**	206−208	32

antimalarial compounds: neocryptolepine **8a** and 2-chloroneocryptolepine **8b**.

The reaction of **1a**−**d** and **2a**,**b** in refluxing methanolic KOH affords **3** as a yellow precipitate which renders this procedure ideal for the synthesis of 2-aminoquinolines (Table 1). In addition to spectroscopic and HRMS data (^{1}H NMR, ^{13}C NMR, DEPT 135 ^{13}C NMR, IR, HRMS), the common structural features of **3** were confirmed by X-ray crystallographic analysis of 6,8-dibromo-3-(2-nitrophenyl)quinolin-2-amine **3d** (Figure 1).

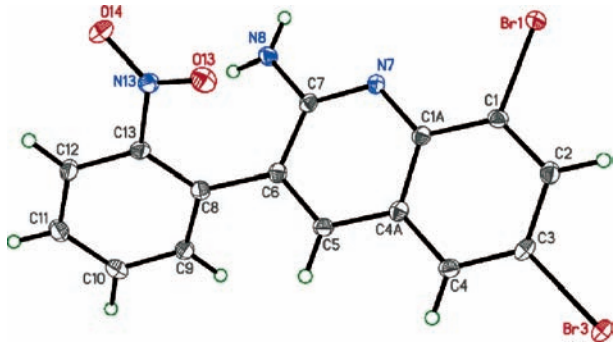
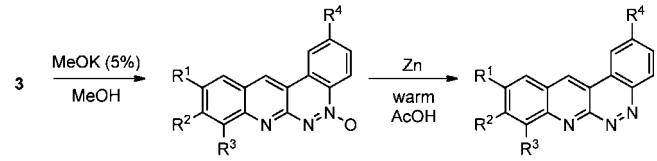


Figure 1. X-ray crystal structure of **3d**.

Syntheses of quinolino[2,3-*c*]cinnoline derivatives **5a**−**f** were achieved via cycloannulation of **3** under basic conditions[3] to afford the corresponding unknown quinolino[2,3-*c*]cinnoline 5-oxides **4** in quantitative yields. Deoxygenation was realized following a literature procedure reported by Boger[4] which makes use of Zn powder in warm AcOH (Scheme 1). In

Scheme 1. Synthesis of Quinolino[2,3-*c*]cinnoline **5**

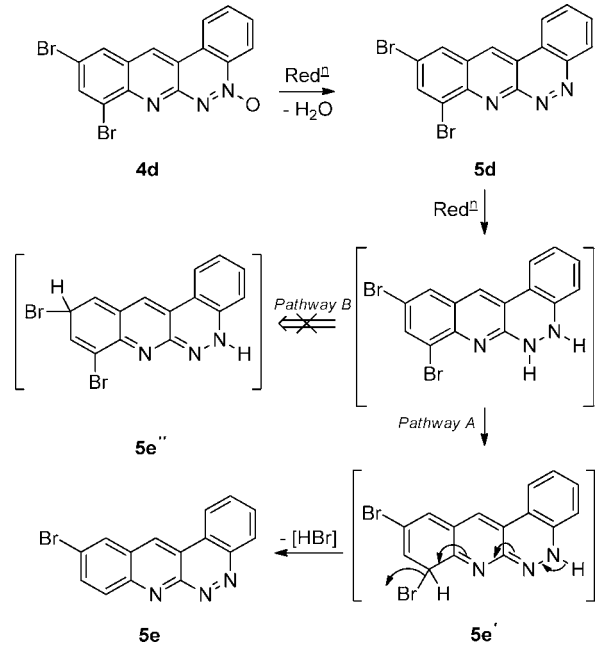


4 5

this series, one interesting result was the deoxygenation of **4d** which afforded two reduced products: 8,10-dibromoquinolino-[2,3-*c*]cinnoline **5d** (38%) and the 10-bromo derivative **5e** (59%). ^{1}H NMR analysis of **5e** indicated the loss of the 8-bromo substituent, as evident by the presence of two singlet peaks at δ 9.40 and δ 8.04 corresponding to protons at C12 and C11, respectively. Equally definitive insight into the structure of **5e** was obtained from analysis of the mass spectrum which indicated the presence of one bromine in **5e** ($[M]^+ = 310.1$ and $[M + 2]^+ = 312.1$).

Our proposed reaction mechanism for **4d** → **5e** is based on two reductive steps followed by an elimination step (Scheme 2). However, the selectivity of this reaction in

Scheme 2. Proposed Reaction Mechanism for the Formation of **5e**



4d 5d 5e'' 5e 5e'

eliminating the 8-bromo substituent rather than the 10-bromo substituent (or a mixture of both options) requires explana-

(2) (a) Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141. (b) Larsen, R. D.; Cai, D. Product Class 3: Quinolines. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Black, D. S., Ed.; Thieme: Stuttgart, NY, 2005; Vol. 15, pp 389−550. (c) Manske, R. H. F.; Kukla, M. *Org. React.* **1953**, *7*, 59. (d) Bergstrom, F. W. *Chem. Rev.* **1944**, 153.

(3) (a) Scobie, M.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1993**, 1756. (b) Scobie, M.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1994**, 2451. (c) Shepherd, T.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 495. (d) Shepherd, T.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 501. (e) Shepherd, T.; Smith, D. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 507. (f) Arshad, A.; Brand, F. A.; Johnston, D.; Smith, D. M. *J. Chem. Res. (S)* **1980**, 208.

(4) Boger, D. L.; Coleman, R. S.; Panek, J. S.; Yohannes, D. *J. Org. Chem.* **1984**, *49*, 4405.

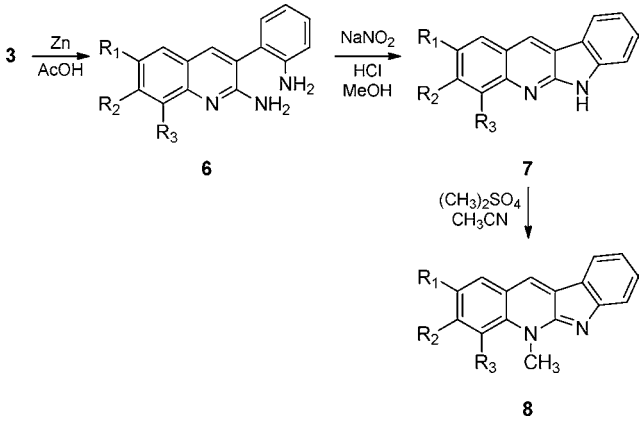
tion. It is suggested that this selectivity arises from the formation of the more stable intermediate **5e**′ (pathway A having four conjugated double bonds, both endo and exo) rather than intermediate **5e**″ (pathway B having only three conjugated double bonds).

In a recent paper by González et al., deoxygenation of a series of *N*-heteroarene *N*-oxides was carried out utilizing short C-chain alcohols as solvent in the presence of a base, such as sodium alkoxide.[5] The reaction conditions reported were relatively harsh, requiring high temperature (120−160 °C). A deoxygenation reaction using 5% methanolic KOH with heating to reflux (65 °C) for 30 min and then at room temperature overnight was carried out. To our good surprise, this method was successful in effecting both cyclization **3c**,**e** → **4c**,**e** and subsequent deoxgenation **4c**,**e** → **5e**,**c** in quantitative yields. In contrast, these same reaction conditions led to the cyclization of **3a**,**d** → **4a**,**d** but did not concomitantly give reduced products **5a**,**d**.

2-Amino-3-(2-nitroaryl)quinolines **3** offer a strategic route toward the preparation of the natural product neocryptolepine **8a** as well as the potential for preparing some of its derivatives (**8b**,**c**). Although several pathways have been developed for the synthesis of **8**,[6] they suffer from the use of sensitive catalysts, low overall yields, or lengthy synthetic routes.

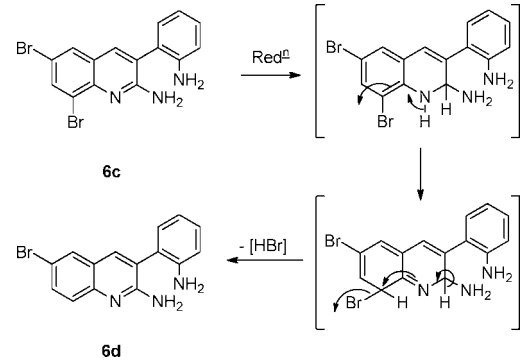
The key step in our preparation of **8** lies in reducing **3** (Zn/acetic acid, 10−15 min) to the corresponding 3-(2-aminophenyl)quinolin-2-amines **6**, in good to moderate yields (Table 2). However, the reduction of 6,8-dibromo-3-(2-nitrophenyl)quinolin-2-amine **3d** was rather intriguing as it generated two reduced products depending on the reaction conditions used: 3-(2-aminophenyl)-6,8-dibromoquinolin-2-amine **6c** (H_2/Pd/C or Zn (1 equiv)/AcOH) was obtained, whereas excess Zn (Zn (18 equiv)/AcOH) yielded the monobromo **6d**. Our postulated mechanism for this interesting reductive elimination of bromine is depicted in Scheme 3. The postulated intermediate, leading to the 6-bromo-substituted product **6d** rather than the 8-bromo isomer, rests upon the argument that this intermediate has three conjugated double bonds in contrast to two for the alternative intermediate which would have led supposedly to the 8-bromo isomer. This argument for selective debromination is analogous to that, advanced above, for the formation of product **5e** via intermediate **5e**′ (Scheme 2).

Table 2. Route toward the Synthesis of **8**



6	R^1	R^2	R^3	**7**	yield (%)	**8**	yield(%)
a	H	H	H	**a**	54	**a**	70
b	Cl	H	H	**b**	55	**b**	73
c	Br	H	Br	**c**	79	**c**	0
d	Br	H	H	-	-	-	-

Scheme 3. Postulated Mechanism for the Formation of **6d**



(5) Bjørsvik, H.; Gambarotti, C.; Jensen, V. R.; Gonzalez, R. R. *J. Org. Chem.* **2005**, *70*, 3218.

(6) (a) Molina, P.; Alajarín, M.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747. (b) El Sayed, I.; Van der Veken, P.; Steert, K.; Dhooghe, L.; Hostyn, S.; Van Baelen, G.; Lemière, G.; Maes, B. U. W.; Cos, P.; Maes, L.; Joossens, J.; Haemers, A.; Pieters, L.; Augustyns, K. *J. Med. Chem.* **2009**, *52*, 2979. (c) Jonckers, T. H. M.; Van Miert, S.; Cimanga, K.; Bailly, C.; Colson, P.; De Pauw-Gillet, M. C.; Van den Heuvel, H.; Claeys, M.; Lemière, F.; Esmans, E. L.; Rozenski, J.; Quirijnen, L.; Maes, L.; Dommisse, R.; Lemière, G.L. F.; Vlietinck, A.; Pieters, L. *J. Med. Chem.* **2002**, *45*, 3497. (d) Engqvist, R.; Bergman, J. *Org. Prep. Proced. Int.* **2004**, *36*, 386. (e) Schmittel, M.; Steffen, J. P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2371.

(7) Altun, Y. *J. Solution Chem.* **2004**, *33*, 479.

(8) Kaljurand, I.; Kuett, A.; Soovaeli, L.; Rodima, T.; Maeemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

(9) Ho, T. L.; Jou, D. G. *Helv. Chim. Acta* **2002**, *85*, 3823.

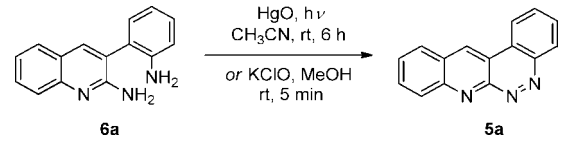
(10) Guo, W.; Jiang, Q.-J.; Lu, F.; Yang, D.-Q. *Chin. J. Synth. Chem.* **2004**, *12*, 12.

to prepare 2,4-dibromoneo-cryptolepine were unsuccessful. Apparently, substitution at position 4 hinders and deactivates the quinolino-nitrogen as a nucleophile and thus prevents N-methylation.[12]

Finally, an interesting reaction of 3-(2-aminophenyl)quinolin-2-amines **6a** was accomplished following a procedure reported by Farhadi et al. where primary aromatic amines are subjected to a selective photochemical oxidation, in the presence of mercury(II) oxide HgO as the photo-oxidant, to produce the corresponding azoaromatic compounds.[13] We employed a modification of this procedure by stirring a solution of **6a** and solid HgO in sunlight for 6 h and isolated the corresponding quinolino[2,3-*c*]cinnoline **5a**. The same product was also obtained in an easy and more efficient procedure when we oxidized a methanolic solution of **6a** with potassium hypochlorite at room temperature (Scheme 4).

In conclusion, the synthesis of a series of new 2-amino-3-(2-nitroaryl)quinolines **3**, quinolino[2,3-*c*]cinnoline 5-oxides **4**, and quinolino[2,3-*c*]cinnolines **5** has been achieved in relatively good yields. Moreover, we report a new and easy method for the synthesis of the naturally occurring and biologically active neocryptolepine (**8**) starting from the previously unknown 3-(2-aminophenyl)-quinolin-2-amine **6a**.

Scheme 4. Photoassisted Oxidation of **6a**



6a **5a**

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Supporting Information Available: Experimental procedures for the synthesis of compounds **1**−**8** are detailed. In addition, spectroscopic data for compounds **1a**−**d**, **3a**−**e**, **4a**−**e**, **5a**−**f**, **6a**−**e**, **7a**−**c**, and **8a**,**c** as well as X-ray data for **3d** are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Teng, C.; Yang, X.; Yuan, C.; Li, C.; Chen, R.; Tian, H.; Li, S.; Hagfeldt, A.; Sun, L. *Org. Lett.* **2009**, *11*, 5542.

(12) Van Miert, S.; Jonckers, T.; Maes, L.; Vlietinck, A.; Dommisse, R.; Lemière, G.; Pieters, L. *Acta Hortic.* **2005**, *677*, 91.

(13) Farhadi, S.; Zaringhadam, P.; Sahamieh, R. Z. *Acta Chim. Slov.* **2007**, *54*, 647.