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N-Bromosuccinimide as an efficient catalyst for the synthesis of indolo[2,3-*b*]quinolines

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ABSTRACT

The use of *N*-bromosuccinimide as a catalyst promoted the synthesis of polycyclic indolo[2,3-*b*]quinoline derivatives in good to high yields in the reactions of various aryl amines with indole-3-carbaldehyde at room temperature under mild conditions.

Heterocyclic compounds containing an indole moiety have been found in many biologically important natural products.[1,2] Indoloquinoline alkaloids have received significant attention in recent years because they are known to act as DNA intercalating agents[3] and exhibit antimalarial properties.[4,5] The roots of *Cryptolepis sanguinolenta*, which is a rich source of indoloquinoline alkaloids, have traditionally been used by Ghanaian healers to treat a variety of health disorders.[6] Cryptolepine (5-methyl-5*H*-indolo[3,2-*b*]quinoline) (**1**), neocryptolepine (cryptotackieine, 5-methyl-5*H*-indolo[2,3-*b*]quinoline) (**2**), and isocryptolepine (cryptosanguinolentine, 5-methyl-5*H*-indolo[3,2-*c*]quinoline) (**3**) are three examples of the thirteen characterized alkaloids from *Cryptolepis sanguinolenta* (Fig. 1).[7,8] Chemically, these compounds are isomeric indoloquinolines, but more importantly, the two linearly- (**1** and **2**) and angularly-fused (**3**) isomers possess interesting antiplasmodial activity.[4,9] Recently, the synthesis of 6*H*-indolo[2,3-*b*]quinoline was accomplished by simple and useful procedures: iodine in diphenyl ether[10] or RuY in 1,4-dioxane.[11]

Herein, we report a convenient and simple method for the synthesis of indolo[2,3-*b*]quinolines from various aryl amines and indole-3-carbaldehyde in the presence of *N*-bromosuccinimide in good to high yields under mild conditions (Scheme 1).

Initially, we decided to examine various catalysts for the synthesis of 6*H*-indolo[2,3-*b*]quinoline as a model compound (see Table 2, entry 1). In the absence of catalyst no product was observed, even after a prolonged reaction time. We investigated the effects of various catalysts including NBS, TBBDA (*N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide), PBBS [poly (*N*,*N*′-dibromo-*N*-ethylbenzene-1,3-disulfonamide)],[12] etc., under various conditions. The results are summarized in Table 1. The best result was achieved using *N*-bromosuccinimide (Table 1, entry 2). We next investigated the scope of this new protocol in reactions of various aryl amines and indole-3-carbaldehyde using *N*-bromosuccinimide (0.67 mmol) under optimized conditions (Table 2, entries 1–9). Also, the products using aniline and 1-aminonaphthalene (Table 2, entries 1–2) are the same as the products from these two amines obtained in the previously published work.[10]

Mechanistically, it is likely that *N*-bromosuccinimide releases Br^+ in situ, which acts as an electrophilic species and the mechanism shown in Scheme 2 is proposed for the synthesis of the indolo[2,3-*b*]quinoline derivatives.[10,11] Initially, *N*-bromosuccinimide catalyzed the formation of an imine and then a 3-bromo-indolinium cation as intermediates. After nucleophilic attack by a second mole of aniline, intramolecular cyclization and oxidation lead to

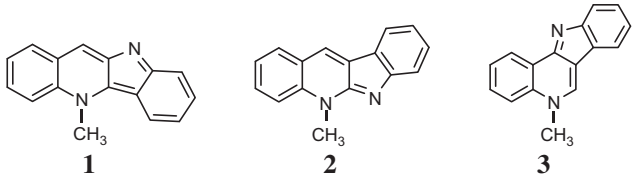

Figure 1. Structures of cryptolepine (**1**), neocryptolepine (cryptotackieine) (**2**), and isocryptolepine (cryptosanguinolentine) (**3**).

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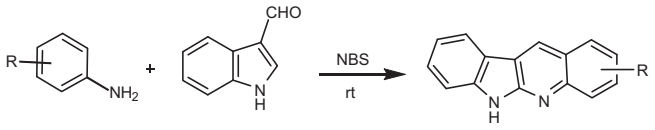


Scheme 1. Synthesis of indolo[2,3-*b*]quinoline derivatives.

the indoloquinoline derivatives. Also, we prepared imine, separately by the reaction between indole-3-carbaldehyde (1 mmol) and aniline (1 mmol) in the presence of NBS in acetonitrile at room temperature, and applied it to the reaction with the second mole of aniline. We obtained the corresponding indoloquinoline. But, the yield of this procedure (step by step) was lower than the one-pot procedure that we describe in this Letter.

In conclusion, we have developed a simple procedure for the synthesis of novel polycyclic indolo[2,3-*b*]quinoline derivatives from the reaction of various aryl amines and indole-3-carbaldehyde in the presence of *N*-bromosuccinimide as the catalyst at room temperature under mild conditions.

Synthesis of 6*H*-indolo[2,3-*b*]quinoline (Table 2, entry 1); typical procedure

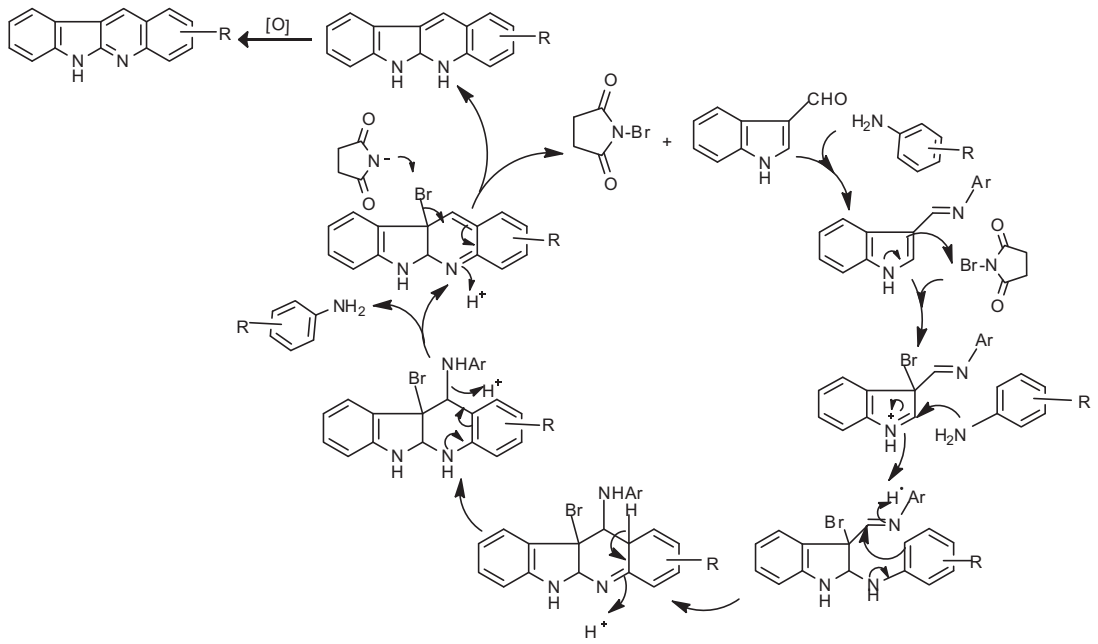
To a stirred mixture of aniline (0.372 g, 4 mmol) and indole-3-carbaldehyde (0.290 g, 2 mmol) was added *N*-bromosuccinimide (0.12 g, 0.67 mmol), [for solid aryl amines a few drops (1 mL) of MeCN were added]. The progress of the reaction was monitored by TLC (8:4, *n*-hexane/acetone). After completion of the reaction, MeCN (10 mL) was added. The solid was filtered off, washed with MeCN, and dried. The residue was recrystallized from *n*-hexane/EtOAc (80:20) to afford the pure product. Evaporation of the MeCN under reduced pressure returned the catalyst.

Spectral data for 3,7-dihydro-2*H*-[1,4]dioxino[2,3-*g*]indolo[2,3-*b*]quinoline (Table 2, entry 3): White solid (60%); mp 160-162 °C; [Found: C, 73.83; H, 4.31; N, 10.10, $C_{17}H_{12}N_2O_2$ requires C, 73.91; H, 4.37; N, 10.14%]; IR (KBr) (ν_{max}, cm^{-1}) 3395, 3105, 2926, 2871, 1600, 1577, 1494, 1456, 1304, 1244, 1115, 1066, 953, 888, 748 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H, NH), 8.68 (s, 1H, Ar-H), 8.37 (d, J = 8 Hz, 1H, Ar-H) 7.96 (s, 1H, Ar-H), 7.48 (d, J = 4 Hz, 1H, Ar-H), 7.25-7.15 (m, 2H, Ar-H), 6.78 (s, 1H,

Table 1
Optimization of the reaction between aniline and indole-3-carbaldehyde

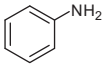
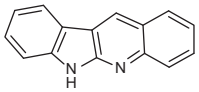
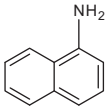
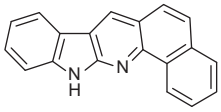
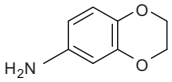
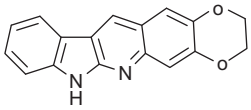
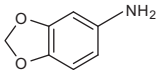
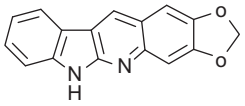
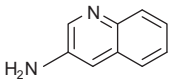
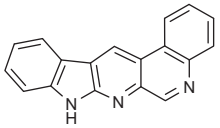
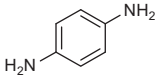
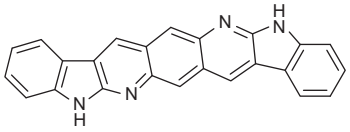
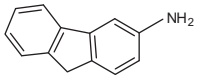
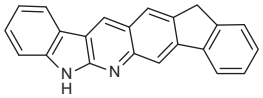
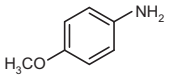
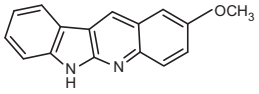
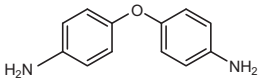
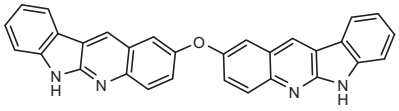
Entry	Catalyst	Amount of catalyst (mol%) (g)	Conditions	Time (min)	Yield[a] (%)
1	NBS	0.42	Solvent-free, rt	220	40
2	NBS	0.67	Solvent-free, rt	285	90
3	NBS	1.12	Solvent-free, rt	94	50
4	NBS	0.67	CH_3CN, rt	196	54
5	NBS	0.56	EtOH-H_2O, rt	230	50
6	TBBDA	0.09	Solvent-free, rt	67	Trace
7	TBBDA	0.21	Solvent-free, 60 °C	270	30
8	TBBDA	0.01	CH_3CN, reflux	272	43
9	PBBS	0.1	Solvent-free, rt	53	55
10	Oxalic acid	1.55	Solvent-free, rt	340	0
11	CAN	0.18	Solvent-free, rt	120	0
12	$CuNO_3$	0.54	Solvent-free, rt	120	40
13	No catalyst	—	Solvent-free, rt	150	0
14	No catalyst	—	Solvent-free, 60 °C	150	0

[a] Isolated yield.



Scheme 2. Proposed mechanism for the preparation of indolo[2,3-*b*]quinoline derivatives.

Table 2
Synthesis of polycyclic indolo[2,3-*b*]quinoline derivatives

Entry	Substrate	Product[a]	Time (min)	Yield (%)	Ref.
1			285	90	10
2			180	56	10
3			420	60	–
4			390	61	–
5			390	70	–
6			150	93	–
7			555	95	–
8			285	50	–
9			135	72	–

[a] Products were characterized from their physical properties, by comparison with authentic samples, and by spectroscopic methods.

Ar-H), 4.26 (s, 4H, CH_2–CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 64.4, 64.6, 109.3, 112.4, 114.5, 115.4, 117.6, 121.2, 122.3, 123.2, 125.2, 133.5, 137.5, 141.3, 144.0, 147.3, 154.5; MS *m/z* (%): 277 (MH^+, 32), 249 (31), 221 (260), 193 (100), 167 (36), 142 (40), 128 (21), 76 (7).

Acknowledgements

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References and notes

1. Du, D.; Li, L.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 4379.
2. Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906.
3. Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; Pascula-Terasa, B.; Gago, F.; Rodrigo, M. M.; Ballestros, M. *J. Org. Chem.* **1996**, *61*, 5587.
4. Cimanga, K.; De Bruyne, T.; Pieters, L.; Vlietinck, A. J.; Turger, C. A. *J. Nat. Prod.* **1997**, *60*, 688.
5. Paulo, A.; Gomes, E. T.; Steele, J.; Warhurst, D. C.; Houghton, P. *J. Planta Med.* **2000**, *66*, 30.
6. Molina, P.; Alazarin, M.; Vidal, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1277.
7. Cimanga, K.; De Bruyne, T.; Pieters, L.; Claeys, M.; Vlietinck, A. *Tetrahedron Lett.* **1996**, *37*, 1703.
8. Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N.; Phoebe, C. H.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239.
9. Grellier, P.; Ramiaramanana, L.; Millerioux, V.; Deharo, E.; Schrével, J.; Frappier, F.; Trigalo, F.; Bodo, B.; Pousset, J.-L. *Phytother. Res.* **1996**, *10*, 317.
10. Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 8369.
11. Khorshidi, A.; Tabatabaeian, K. *J. Mol. Catal. A: Chem.* **2011**, *344*, 128.
12. Ghorbani-Vaghei, R.; Jalili, H. *Synthesis* **2005**, 1099.