A Facile and Expeditious Synthesis of Cryptosanguinolentines

Dalip Kumar,* Maruthi Kumar. N., and V. S. Rao
Chemistry Group, Birla Institute of Technology and Science, Pilani-333031, India

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A simple and efficient synthesis of naturally occurring cryptosanguinolentines is described. Neat reaction of easily accessible 1-methyl-1,2,3,4-tetrahydroquinolin-4-ones and aryl hydrazines in the presence of *p*-toluenesulfonic acid at 100 °C rapidly afforded cryptosanguinolentines in very good yields.

The synthesis of heteroaromatic alkaloids is of great importance and has generated significant interest among organic chemists as these alkaloids are known to be potent medicinal compounds. For example, cryptosanguinolentine is an important indoloquinoline alkaloid isolated from *cryptolepis sanguinolenta*[1] and used in folk medicine as an antimalarial agent. Particularly, isomeric indoloquinolines such as cryptolepine and neocryptolepine are also found to display antiplasmodial activity (Figure 1).[2] Some indoloquinoline alkaloids are very good DNA intercalators[2] and can inhibit DNA replication and transcription. Thus, synthesis of cryptosanguinolentines is of prime importance and consequently, various methods have been developed for their synthesis.

Preparation of cryptosanguinolentines by Molina et al.[3,4] involved the intramolecular reaction of iminophosphorane with isocyanate. Subsequently, these authors have also reported their preparation by thermocyclization of intermediate 1-methyl-3-(*o*-azidophenyl)quinolin-2-ones followed by the reduction of resulting indoloquinoline. In a similar approach Trecourt et al.[5] have also used thermolysis of 3-(2-azidophenyl)quinolines to prepare cryptosanguinolentines. An alternate approach by Jonckers et al.[6] involved the selective Buchwald–Hartwig amination followed by an intramolecular arylation reaction in three synthetic steps with 58% overall yield. Timari et al.[7] have prepared cryptosanguinolentines in five steps using palladium-catalyzed coupling of *N*-pivaloylaminophenylboronic acid with 3-bromoquinoline. The three-step synthesis by Mohan et al.[8] involves preparation of key intermediate indoloquinoline by the reaction of 4-hydroxy-1-methyl-1*H*-quinolin-2-one with phenylhydrazine; which upon treatment with $POCl_3$ followed by dehalogenation afforded the product in 28% overall yield. Recently, Mohan et al. have also reported photocyclization of a Schiff's base[9a] and anilinoquinolines[9b] to afford cryptosanguinolentines in 47.3% and 47.9% overall yields, respectively. However, most of the existing protocols involve use of costly starting materials or reagents, multiple synthetic steps, longer reaction time, harsh reaction conditions with moderate yields of the product.

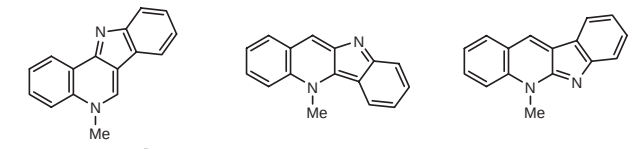


Figure 1. Structures of some indoloquinoline alkaloids.

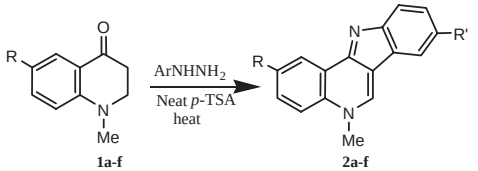
There is an increasing interest in developing eco-friendly organic reactions due to the growing concern for the influence of organic solvents on the environment.[10] In this context, the replacement of toxic and volatile conventional organic solvents as reaction media with environmentally acceptable alternatives such as water, fluorous media, ionic liquids, PEG etc. is highly desirable. Particularly, reactions under solvent-free conditions are of tremendous importance in modern organic synthesis as it avoids the use of toxic solvents and the formation of undesired products and generally afford the desired products in greater yield.[10] In view of the environmental constraints and interesting biological activities displayed by cryptosanguinolentines, it is desirable to develop a benign and facile protocol for their syntheses. Inspired by recently reported[11] easy and short synthesis of 1,2,3,4-tetrahydroquinolones, we envisioned this to be a starting material for the Fischer indole reaction with arylhydrazines to obtain cryptosanguinolentine and its analogues.

In our efforts to prepare cryptosanguinolentine by the reaction of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one (**1a**) and phenylhydrazine under solvent-free conditions,[12] initially we screened different acids at various temperatures. At lower temperatures (<100 °C) the reaction was very sluggish and resulted in poor yield of cryptosanguinolentine. Among the acids, *p*-TSA was found superior in terms of reaction time and product yield (Table 1). The neat reaction of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one (**1a**) with phenylhydrazine at 100 °C in the presence of *p*-TSA afforded cryptosanguinolentine in 83% yield (Scheme 1).[13] After completion of the reaction, cryptosanguinolentine **2a** was isolated simply by neutralization of the reaction mixture. The protocol was further extended to the preparation

Table 1. Reaction of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one (**1a**) and phenylhydrazine in the presence of various acid catalysts

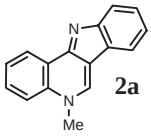
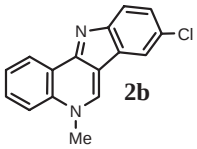
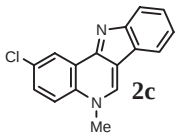
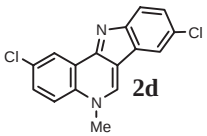
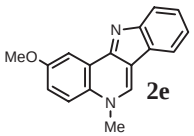
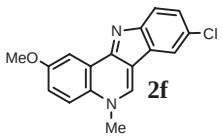
Acid catalysts[a]	Reaction time /min	Product yield /%[b]
$ZnCl_2$	120	40
$SnCl_4$	90	35
TFA	240	40
Phosphotungstic acid	150	28
p-TSA	20	83
$FeCl_3$	120	30

[a]1.1 Equivalent used. [b]Yield of pure product.

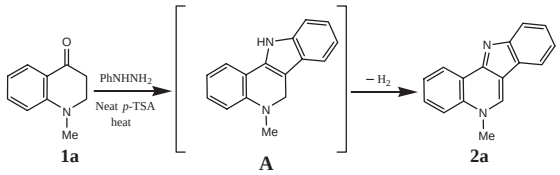


Scheme 1. Synthesis of cryptosanguinolentines.

Table 2. Solvent-free synthesis of cryptosanguinolentines **2**

Entry	Product (**2a–2f**)[a]	Time /min	Yield /%[b]
1	 **2a**	20	83
2	 **2b**	25	77
3	 **2c**	25	74
4	 **2d**	30	84
5	 **2e**	25	82
6	 **2f**	30	78

[a]Products were characterized by NMR, IR, and mass spectrometry analysis. [b]Yields of pure products.



Scheme 2. Proposed reaction pathway for the synthesis of **2**.

of various substituted cryptosanguinolentines **2b–2f** in very good yields (77–84%, Table 2). Substrates, 1-methyl-1,2,3,4-tetrahydroquinolin-4-ones **1** and arylhydrazines either with electron-donating or -withdrawing groups reacted well under the reaction conditions. The scope of this useful synthetic transformation was further broadened by the successful reaction of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one **1** (10 mmol) and phenylhydrazine at larger scale affording cryptosanguinolentine (**2a**) in 80% yield.

Mechanistically, Fischer indole cyclization of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one (**1a**) with phenylhydrazine, initially formed intermediate **A**, which upon dehydrogenation produces cryptosanguinolentine (**2a**) (Scheme 2). Dehydrogenation of intermediate **A** generates more stable cryptosanguinolentine **2a** in which both the nitrogens are in conjugation. Similar dehydrogenations are also reported in the literature under the influence of heat, light, or oxygen.[9,14]

In conclusion, we have developed a novel, short, and high yielding solvent-free synthesis of biologically important cryptosanguinolentine and its analogues from easily accessible starting materials. Further exploration of this useful protocol towards the synthesis of biologically potent compounds is in progress.

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References and Notes

1 a) M. H. M. Sharaf, P. L. Schiff, A. N. Tackie, C. H. Phoebe, G. E. Martin, *J. Heterocycl. Chem.* **1996**, *33*, 239. b) K. Cimanga, T. D. Bruyne, L. Pieters, M. Claeys, A. Vlietinick, *Tetrahedron Lett.* **1996**, *37*, 1703. c) G. C. Kirby, A. Paine, D. C. Warhurst, B. K. Noamese, J. D. Phillipson, *Phytotherapy Res.* **1995**, *9*, 359. d) K. Cimanga, T. D. Bruyne, L. Pieters, A. Vlietinck, C. A. Turger, *J. Nat. Prod.* **1997**, *60*, 688. e) J.-L. Pousset, M.-T. Martin, A. Jossang, B. Bodo, *Phytochemistry* **1995**, *39*, 735.

2 a) L. Dassonneville, K. Bonjean, M. C. D. Pauw-Gillet, P. Colson, C. Houssier, J. Quetin-Leclercq, L. Angenot, C. Bailly, *Biochemistry* **1999**, *38*, 7719. b) W. Peczynska-Czoch, F. Pognan, L. Kaczmarck, J. Boratyriski, *J. Med. Chem.* **1994**, *37*, 3503. c) G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila, H. Junjappa, *J. Org. Chem.* **2004**, *69*, 5760.

3 P. Molina, M. Alajarin, A. Vidal, *Tetrahedron* **1990**, *46*, 1063.

4 P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron Lett.* **1999**, *40*, 7275.

5 F. Trecourt, F. Mongin, M. Mallet, G. Queguiner, *Synth. Commun.* **1995**, *25*, 4011.

6 T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemiere, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett* **2003**, 615.

7 G. Timari, T. Soos, G. Hajos, *Synlett* **1997**, 1067.

8 T. Dhanabal, R. Sangeetha, P. S. Mohan, *Tetrahedron Lett.* **2005**, *46*, 4509.

9 a) R. N. Kumar, T. Suresh, P. S. Mohan, *Tetrahedron Lett.* **2002**, *43*, 3327. b) T. Dhanabal, R. Sangeetha, P. S. Mohan, *Tetrahedron* **2006**, *62*, 6258.

10 a) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **1998**. b) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, **2000**. c) K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025. d) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629.

11 a) K. M. Kasiotis, N. Fokialakis, S. A. Haroutounian, *Synthesis* **2006**, 1791. b) S. Chandrasekhar, K. Vijeender, C. Sridhar, *Tetrahedron Lett.* **2007**, *48*, 4935.

12 K. Matsumoto, A. Tanaka, I. Yukio, N. Hayashi, M. Toda, R. A. Bulman, *Heterocycl. Commun.* **2003**, *9*, 9.

13 General experimental procedure: A mixture of 1-methyl-1,2,3,4-tetrahydroquinolin-4-one **1** (1.0 mmol), arylhydrazine (1.0 mmol), and *p*-toluenesulfonic acid (1.1 mmol) was heated at 100 °C for 20–30 min (Table 2). After completion of reaction, the mixture was allowed to cool at room temperature and the solid residue was taken into dilute solution of sodium bicarbonate. The solid product was filtered, washed with water (10 mL) and recrystallized from ethanol to afford pure compound (**2a–2f**).[15]

14 a) G. R. Lenz, *J. Org. Chem.* **1934**, *90*, 1325. b) K. A. Muszkat, E. Fischer, *J. Chem. Soc. B* **1967**, 662.

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