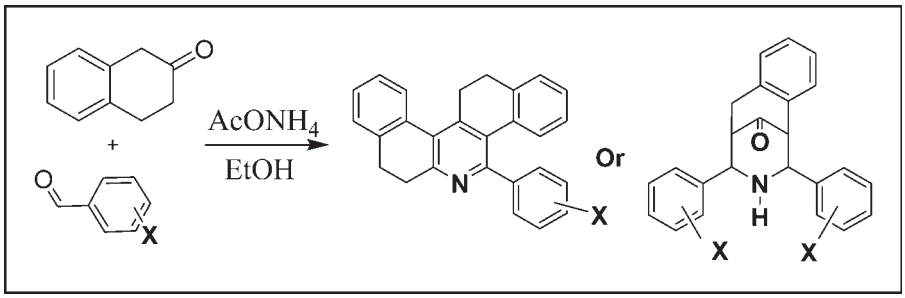
Dual Behavior of 2-Tetralone: A New Approach for the Synthesis of 5-Aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine

Kulathu Iyer Sathiyanarayanan,[a]* Natesan Sundaramurthy Karthikeyan,[a] Paduthapillai Gopal Aravindan,[b] Seenan Shanthi,[a] Ravindranath S. Rathore,[c] and Chang Woo Lee[d]

[a]Chemistry Division, School of Science and Humanities, VIT University, Vellore 632 014, India
[b]Physics Division, School of Science and Humanities, VIT University, Vellore 632 014, India
[c]School of Biotechnology, Devi Ahilya University, Indore 452 001, India
[d]College of Environment and Applied Chemistry, Kyung Hee University, Yongin 449-701, Korea
*E-mail: sathiya_kuna@hotmail.com

Received February 16, 2009
DOI 10.1002/jhet.191
Published online 2 November 2009 in Wiley InterScience (www.interscience.wiley.com).



The one-pot reaction of 2-tetralone with ammonium acetate and substituted benzaldehydes affords in a good yield of 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine or 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one. The course of the reaction seems to be dictated by the position of the substituents present on the benzaldehyde ring.

J. Heterocyclic Chem., **46**, 1142 (2009).

INTRODUCTION

Phenanthridines, an important class of heterocyclic compounds in medicinal chemistry, are attractive synthetic targets due to their widespread occurrence in nature and broad range of biological activities, including anti-tumor and anti-viral activities [1–7]. Phenanthridine derivatives exhibit interesting pharmacological properties related to the planarity of the system. Benzophenanthridines are reported as compounds with topoisomerase I-targeting activity and cytotoxicity [8].

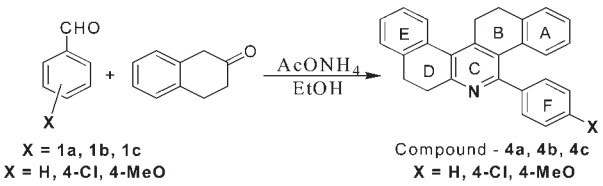
In addition, the high charge mobility of this heterocyclic system provides pronounced photoconducting, optoelectrical switching, and photovoltaic properties [9–11], which are key features in the field of dye lasers and electroluminescence [12,13]. Therefore, during the last few years, phenanthridines have gained much attention because of their promising applications in the development of optical materials, information recordings, such as, holography, lithographic plates for printing, and electric equipment [14].

The literature preparations of the phenanthridine ring system have disadvantages, such as, lengthy syntheses, low yields, and structurally complicated precursors [8,15–20]. Even a synthesis involving a few steps from simple precursors such as formaldehyde and 2-methylbenzonitrile affords benzo[c]phenanthridine in a 6% overall yield [15]. In this study, we found that one-step reaction of benzaldehyde or 4-substituted benzaldehydes, ammonium acetate, and 2-tetralone gave 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine (Scheme 1). On the other hand, the one-step reaction of 2-substituted benzaldehydes, ammonium acetate, and 2-tetralone gave 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones (Scheme 2).

In spite of their importance, only very few of them involve less than a few steps [16,20–22]. On the contrary, this study involves single step. Hence, the authors wish to explore a new and more versatile synthetic route for 5-aryl-7,8,13,14-tetrahydrodibenzo [*a*,*i*]phenanthridine.

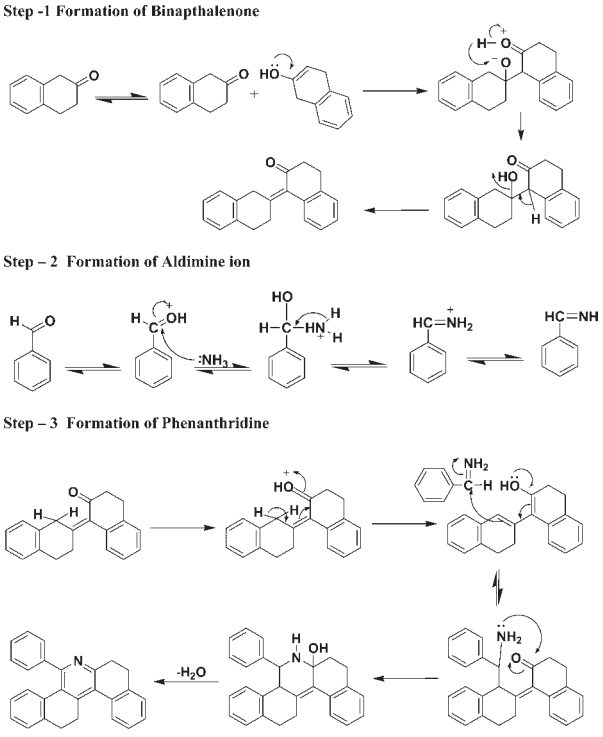
The preparation of 5-phenyltetrahydrodibenzo[*a*,*i*]phenanthridine (4) and 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5) was accomplished by the procedure reported by Noller and Baliah [23] through a simple three-compound reaction involving ammonium acetate (2), benzaldehyde (1), and 2-tetralone (3). We tried to carry out the Mannich reaction as reported in the article. However, we ended up with 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine in the case of parent benzaldehyde and para-substituted benzaldehydes. However, ortho-substituted benzaldehydes yielded 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-ones. The two reactions are not competing with each

Scheme 1

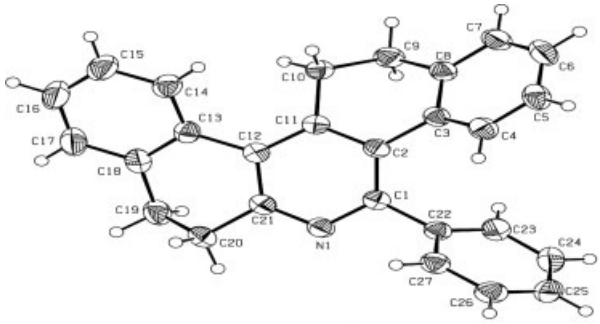


other. We are getting either phenanthridine or azabicyclo[3.3.1]nonan-9-one only. The product formation is exclusive. We are not getting the mixture of products. In Mannich reaction, the active methylene group in the 2-tetralone took part, whereas in the other reaction the enol form of 2-tetralone occurred. This reaction was found to be very easy and useful for synthesizing phenanthridine because other methods now being used are cumbersome and involve more steps (Table 1).

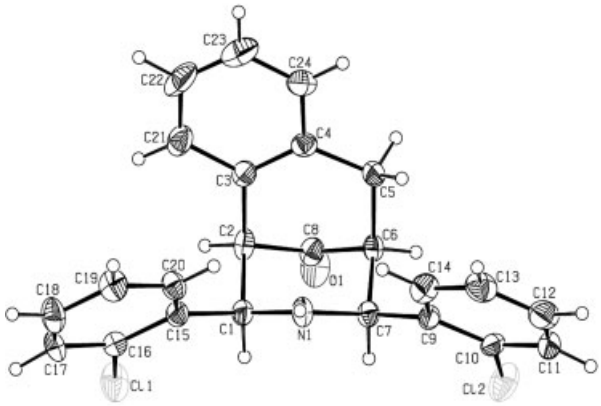
The mechanism for the formation of 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one is already well documented [23]. We are proposing the following mechanism for the formation of phenanthridine derivative. The mechanism proposed is similar to the one reported for the reaction between tetralone and nitrile [20]. All the structures were confirmed by single crystal X-ray analysis.



The parent and para-substituted benzaldehydes give phenanthridine, and ortho-substituted benzaldehydes give azabicyclo[3.3.1]nonan-9-one. This is due to the steric hindrance in the ortho-substituted benzaldehydes and it is clearly shown in the mechanism. The aldimine formation in ortho-substituted benzaldehydes is impossible. Once it is able to form the aldimine then only the formation of phenanthridine is possible otherwise keto form will react with benzaldehyde and ammonium acetate to form azabicyclo[3.3.1]nonan-9-one.



Ortep diagram of compound 4a



Ortep diagram of compound 5d

Even the structures are also confirmed by single crystal X-ray analysis.

In conclusion, the authors developed two short, distinct, and complementary methods for the synthesis of various 5-aryl-7,8,13,14-tetrahydrodibenzo[*a*,*i*]phenanthridine and 2,4-diaryl-6,7-benzo-3-azabicyclo[3.3.1]-nonan-9-one with excellent yield. We believe that the

Scheme 2

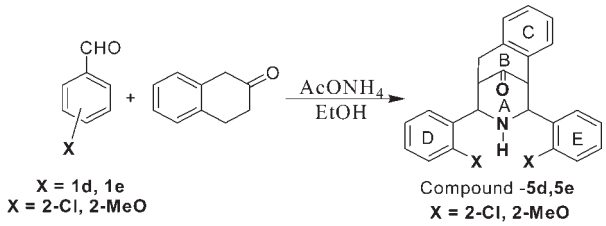


Table 1

Reaction of 2-tetralone with benzaldehydes.

Aldehyde	Product	Yield
Benzaldehyde (1a)	**4a**	86%
p-Chlorobenzaldehyde (1b)	**4b**	74%
p-Methoxybenzaldehyde (1c)	**4c**	76%
o-Chlorobenzaldehyde (1d)	**5d**	68%
o-Methoxybenzaldehyde (1e)	**5e**	65%

reported method provides a potential utility of chemistry in organic synthesis.

EXPERIMENTAL

General procedure. 0.2*M* of respective benzaldehyde was treated with 0.1*M* of 2-tetralone and 0.1*M* of ammonium acetate in 15 mL of ethanol. The mixture was gently warmed in a water bath until the color changed to orange and kept aside for overnight at room temperature. The completion of the reaction was identified with TLC. The solid obtained was separated and the crude compound was purified by silica gel column chromatography using hexane and ethyl acetate as elutant.

Spectral data

5-Phenyl-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4a). Crystal; mp 170°C; IR (KBr): 3057, 2833, 1606, 1549, 1425, 1396, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.76–3.20 (m, 8H), 7.00–7.53 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.79, 27.41, 29.53, 31.38,124.68, 125.60, 126.30, 126.92, 127.25, 127.64, 127.75, 128.33, 128.68, 129.62, 129.80, 130.58, 132.77, 133.04, 136.99, 138.68, 139.43, 139.67, 140.29, 142.06, 145.65, 153.95, 158.08.

5-(p-Chlorophenyl)-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4b). Crystal; mp 178°C; IR (KBr): 3032, 2833, 1605, 1549, 1425, 1358, 1245, 763 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.54 (m, 2H), 2.74–3.26 (m, 6H), 7.12–7.61 (m, 12H); MS (LC-MS): $m/z = 394$ (M^+).

5-(p-Methoxyphenyl)-7,8,13,14-tetrahydrodibenzo[a,i]phenanthridine (4c). Crystal; mp 174°C; IR (KBr) 3032, 2833, 1606, 1549, 1425, 1358, 1245 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 2.50–3.08 (m, 8H), 3.78 (s, 3H), 6.86–6.91 (m, 4H), 7.29–7.32 (m, 8H); MS (LGC-MS): $m/z = 390$ (M^+).

2,4-Di(o-chlorophenyl)-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5d). Crystal; mp 230°C; IR (KBr): 3309, 2846, 1711, 1423, 1243, 751 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.92–3.15 (m, 4H), 3.56 (s, 1H, NH), 4.59–4.62 (d, 1H), 5.73–5.76 (d, 1H), 6.74–7.78 (m, 12H).

2,4-Di(o-methoxyphenyl)-6,7-benzo-3-azabicyclo[3.3.1]nonan-9-one (5e). Crystal; mp 220°C; IR (KBr) 3313, 2832, 1715, 1491, 1243 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.48–2.97 (m, 4H), 3.48 (s, 1H, NH), 3.81–4.01 (s, 6H), 4.52–4.55 (d, 1H), 5.75 (d, 1H), 6.66–7.60 (m, 12H).

REFERENCES AND NOTES

[1] Atwell, G. J.; Baguley, B. C.; Denny, W. A. J Med Chem 1988, 31, 774.

[2] Cappelli, A.; Anzini, M.; Vomero, S.; Mannuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Bruni, G.; Romeo, M. R.; Menziani, M. C.; Benedetti, P. G.; Langer, T. J Med Chem 1998, 41, 728.

[3] Janin, Y. L.; Croisy, A.; Riou, J.-F.; Bisagni, E. J Med Chem 1993, 36, 3686.

[4] Simanek, V. In The Alkaloids; Bross, A., Ed.; Academic: New York, 1985; Vol. 26, p 185.

[5] Suffiness, W. M.; Gordell, G. A. In The Alkaloids; Bross, A., Ed.; Academic: New York,1983; Vol. 25, p 178.

[6] Shamma, M. The Isoquinoline Alkaloids: Chemistry and Pharmacology; Academic Press: New York, 1972.

[7] Shamma, M.; Moniot, J. L. Isoquinoline Alkaloids Research, 1972–1977; Plenum Press: New York, 1978.

[8] Li, D. J.; Zhao, B.; Sim, S. P.; Li, T. K.; Liu, L. F.; LaVoie, E. J. Bioorg Med Chem 2003, 11, 3795.

[9] Zhou, Y.; Baker, W.; Kazmaier, E. P. M.; Buncel, E. Can J Chem 1998, 76, 884.

[10] Gorner, H.; Dopp, D.; Dittmann, A. J Chem Soc Perkin Trans 2 2000, 1723.

[11] Aimone, S. L.; Caram, J. A.; Mirifico, M. V.; Vasini, E. J. J Phys Org Chem 2000, 13, 272.

[12] (a) Kuznetsova, L. P.; Nikol'skaya, E. B.; Sochilina, E. E.; Faddeeva, M. D. Tsitologiya 2001, **43**, 1046; (b) Kuznetsova, L. P.; Nikol'skaya, E. B.; Sochilina, E. E.; Faddeeva, M. D. Chem Abstr 137, 210505.

[13] Hoffmann, T. K.; Leenen, K.; Hafner, D.; Balz, V.; Gerharz, C. D.; Grund, A.; Ballo, H.; Hauser, U.; Bier, H. Anti Cancer Drugs 2002, 13, 93.

[14] (a) Taniguchi, Y.; Koyama, T.; Adachi, C.; Saitou, T.; Satsuki, M.; Shinpo, A.; Tokito, S.; Fujikawa, H.; Noda, K.; Miura, A.; Taga, Y. (Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan) U.S. Pat.20,020,502 (2002); (b) Taniguchi, Y.; Koyama, T.; Adachi, C.; Saitou, T.; Satsuki, M.; Shinpo, A.; Suga, S.; Tokito, S.; Fujikawa, H.; Noda, K.; Miura, A.; Taga, Y. Chem Abstr 136, 348078.

[15] Kock, I.; Clement, B. Synthesis 2005, **7**, 1052.

[16] Churruca, F.; Martin, R. S.; Carril, M.; Urtiaga, M. K.; Solans, X.; Tellitu, I.; Dominguez, E. J Org Chem 2005, 70, 3178.

[17] Feng, W.; Satyanarayana, M.; Tsai, Y.-C.; Liu, A. A.; Liu, L. F.; Lavoie, E. J. Bioorg Med Chem 2008, 16, 8598.

[18] Buden, M. E.; Rossi, R. A. Tetrahedron Lett 2007, 48, 8739.

[19] Kohno, K.; Azuma, S.; Choshi, T.; Nobuhiro, J.; Hibino, S. Tetrahedron Lett 2009, 50, 590.

[20] Herrera, A.; Alvarez, R. M.; Chioua, M.; Chatt, R.; Chioua, R.; Sanchez, A.; Almy, J. Tetrahedron 2006, 62, 2799.

[21] Prado, S.; Michel, S.; Tillequin, F.; Koch, M.; Pfeiffer, B.; Pierre, A.; Leonce, S.; Colson, P.; Baldeyrou, B.; Lansiaux, A.; Bailly, C. Bioorg Med Chem 2004, 12, 3943.

[22] Mehta, K. B.; Kumamoto, K.; Yanagisawa, K.; Kotsuki, H. Tetrahedron Lett 2005, 46, 6953.

[23] Noller, C. R.; Baliah, V. J Am Chem Soc 1948, 70, 3853.