SYNLETT

Accounts and
Rapid Communications in
Synthetic Organic Chemistry

REPRINT

With compliments of the Author

Thieme

An Efficient One-Pot, Three-Component Reaction: Synthesis of Complex-Annelated α-Carbolines via an Intramolecular [3+2]-Dipolar Cycloaddition Reaction

Swarup Majumder, Pulak J. Bhuyan*

Medicinal Chemistry Division, North East Institute of Science & Technology (CSIR), Jorhat 785006, Assam, India
Fax +91(376)2370011; E-mail: pulak_jyoti@yahoo.com

Received 17 March 2011

Abstract: Novel annelated α-carbolines have been synthesized from oxindole using three components in a one-pot procedure involving an intramolecular [3+2]-dipolar cycloaddition reaction of azides to nitriles.

Key words: α-carboline, oxindole, [3+2]-dipolar cycloaddition reaction, β-halo aldehyde, multicomponent reaction

The α-carboline {pyrido[2,3-*b*]indole} system and its annelated (Figure 1) comprise compounds possessing diverse biological activity such as antitumour,[1] anti-HIV,[2] antiviral,[3] anxiolytic, anti-inflammatory, CNS stimulating,[4] and antileukemia activity.[5] Possibly the activities that have attracted most attention to the α-carbolines are CDK-1, CDK-5, and GSK-3 kinase inhibition.[6] Furthermore, certain α-carbolines have found clinical application for treatment of hypertension.[7]

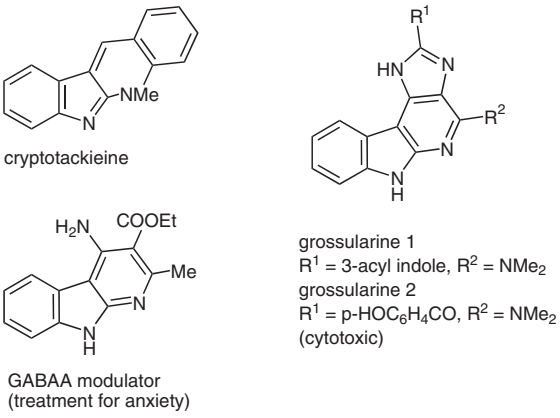


Figure 1

Unsurprisingly, considering the importance of α-carbolines, much effort has been made towards the synthesis of these compounds.[8] Recently, we have reported an efficient method for the synthesis of α-carbolines by exploring the 'tertiary amino effect' reaction strategy.[9]

Five-membered nitrogen heterocycles play an important role in biological systems.[10] Among these,1,2,3,4-tetrazoles have received considerable attention due to their wide range of biological activity and as important synthetic precursors.[11] These nitrogen-rich ring systems are also used in propellants and explosives.[12]

Cycloaddition reactions[13] allow the direct construction of new rings with a variety of substituents by simple addition of two or more reagents. Within this class, inter- and intramolecular dipolar cycloaddition reactions have found extensive use as efficient regio- and stereoselective methodologies.[14] With the current emphasis towards green chemistry, chemical processes with high atom economy have received growing attention from the scientific community. The [3+2]-dipolar cycloaddition of azides to nitriles being a typical case, leading to the formation of 1,2,3,4-tetrazoles.[15]

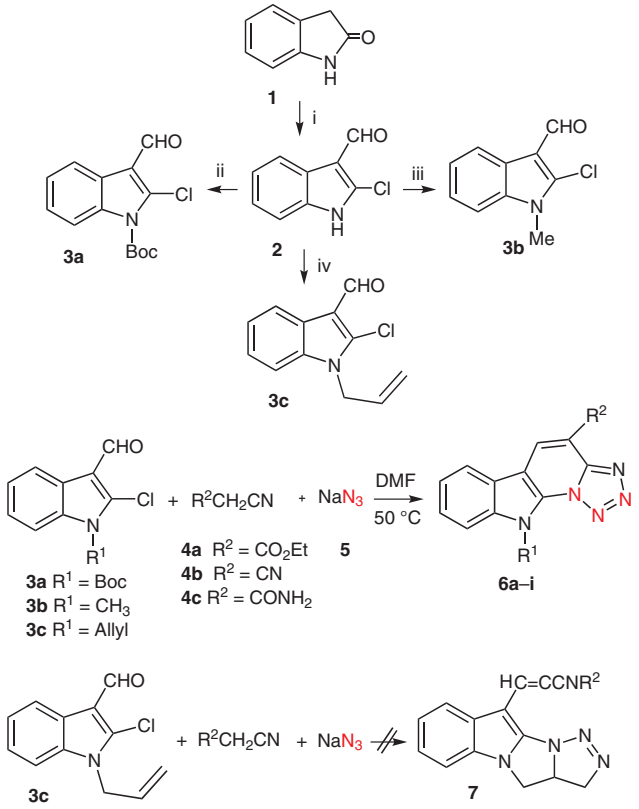
One-pot multicomponent reactions (MCR), by virtue of their convergence have attracted considerable attention.[16] In the past decade there have been developments in three- and four-component reactions and great efforts have been made to develop new MCR.[17]

As part of our continued interest in the area of synthesis of diverse heterocyclic compounds of biological importance,[18] we report herein an efficient method for the synthesis of novel annelated α-carbolines by a three-component, one-pot reaction involving intramolecular [3+2]-dipolar cycloaddition reaction of azides to nitriles (Scheme 1).

Oxoindole (**1**), the starting material in our reaction strategy, on treatment with the Vilsmeier reagent, afforded the key β-halo aldehyde **2**.[9] Boc-protected indole **3a** was prepared in high yield by employing standard Boc-protection protocol using di-*tert*-butyl dicarbonate (Boc_2O).[9] In the three-component reaction[19] equimolar amounts of **3a**, ethyl cyanoacetate **4a**, and sodium azide **5** were treated at 50 °C in the presence of a catalytic amount of triethylamine for three hours using DMF as solvent. The solid obtained on pouring the reaction mixture into water and after workup afforded the compound **6a** in good yield. The structure of the compound was ascertained from spectroscopic and elemental analysis. The ^{1}H NMR spectrum showed the absence of the aldehyde proton and the presence of the ethyl group of the ester. The IR spectrum showed the absence of the cyanide group, which evidenced its involvement in the cycloaddition reaction. The mass spectrum revealed a strong peak at 382.4 [M^+ + Na]. With suitable conditions established for the three-compo-

SYNLETT 2011, No. 11, pp 1547–1550
Advanced online publication: 15.06.2011
DOI: 10.1055/s-0030-1260787; Art ID: D08511ST

nent reaction, a series of compounds **6a–i** was synthesized, utilizing various 2-chloro-3-formyl indoles **3a–c**[20] with alkyl nitriles **4a–c** and sodium azide **5**. The structures of the compounds were determined from their spectroscopic data and elemental analyses (Table 1). Although there was a possibility of the formation of the compound **7** from compound **3c** via intramolecular 1,3-dipolar cycloaddition of the azide to the isolated double bond, we have not observed the formation of such a cycloadduct.

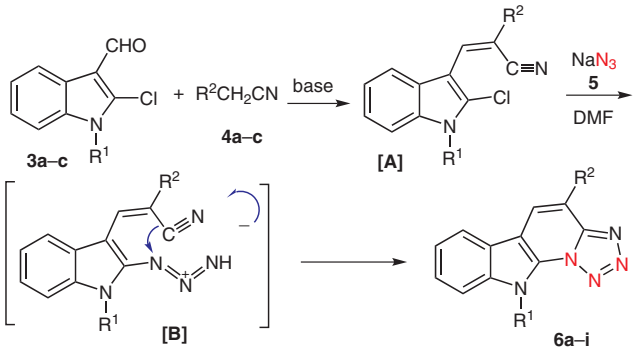


Scheme 1 *Reaction conditions*: (i) DMF, $POCl_3$; (ii) Boc_2O; (iii) MeI, NaH; (iv) allyl bromide, PTC, NaOH.

Initially, we studied the reaction without protecting the nitrogen atom of the indole moiety but nucleophilic substitution by azide did not occur, even under forcing conditions. However, when the nitrogen atom was protected, nucleophilic substitution and the subsequent cyclization steps occurred very smoothly to give the desired compounds in excellent yields. Cyanoacetamides are found to be least reactive.

A plausible mechanism for the reaction is outlined in Scheme 1. Initial Knoevenagel condensation of **3** and **4** in the presence of triethylamine gives intermediate [**A**] which then reacts with sodium azide to give [**B**]. The azide then undergoes an intramolecular [3+2]-dipolar cycloaddition to the pendant cyano group to afford the α-carboline **6**.

The path of the reaction and hence the proposed mechanism was established by performing the reaction stepwise (Scheme 2). First, we treated 1-Boc-2-chloro-3-formyl indole (**3a**) with ethyl cyanoacetate (**4a**) using piperidine as catalyst at room temperature to give the Knoevenagel condensation product [**A**] in quantitative yield.[21] In order to introduce the azido group at the 2-position of the indole molecules, the compound [**A**] was treated with NaN_3 (**5**) in DMF at 50 °C with stirring.[22] However, the intermediate [**B**] could not be isolated but spontaneously underwent intramolecular cycloaddition to the cyanide group to produce the product **6a**. The compound was comparable in all respects to the compound obtained from the three-component reaction.



Scheme 2

The *N*-Boc deprotection could be achieved with standard method.[23] However, we report herein the *N*-Boc-protected compounds because of their very good solubility, which helps in their characterization (N-deprotected compounds have very poor solubility).

Table 1 Synthesis of Compound **6** via the Three-Component Reaction

Product	R^1	R^2	Temp (°C)	Time (h)	Mp (°C)	Yield (%)
6a	BOC	CO_2Et	60	3	222–223	71
6b	Me	CO_2Et	60	3	229–230	70
6c	$CH_2CH{=}CH_2$	CO_2Et	60	3	189–190	67
6d	Boc	CN	50	2.5	175–176	66
6e	Me	CN	50	2.5	181–182	65
6f	$CH_2CH{=}CH_2$	CN	50	2.5	173–174	62
6g	Boc	$CONH_2$	60	3	210–211	55
6h	Me	$CONH_2$	60	3	239–240	59
6i	$CH_2CH{=}CH_2$	$CONH_2$	60	3	207–208	57

In conclusion, we report the synthesis of a novel class of complex α-carboline derivatives from a simple oxindole by exploring the intramolecular [3+2]-dipolar cycloaddition of azides to nitriles using a three-component, one-pot protocol under mild conditions. The pathway for formation of the products in the three-component process was established by performing the reaction stepwise. This very simple protocol for the synthesis of tetracyclic angularly

annelated α-carbolines from readily available starting materials is a valuable addition to the chemistry of α-carbolines in particular and heterocyclic compounds as a whole.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors thank DST, New Delhi for financial support. Mr. S. Majumder thanks CSIR for a research fellowship.

References and Notes

(1) (a) Venkat, R. G.; Qi, L.; Pierce, M.; Robbins, P. B.; Sahasrabudhe, S. R.; Selliah, R. WO 2007076085, **2007**. (b) Arakawa, H.; Monden, Y.; Nakatsuru, Y.; Kodera, T. WO 2003080077, **2003**. (c) Burstein, H. J.; Overmoyer, B.; Gelman, R.; Silverman, P.; Savoie, J.; Clarke, K.; Dumadag, L.; Younger, J.; Ivy, P.; Winer, E. P. *Invest. New Drugs* **2007**, *25*, 161.

(2) (a) Li, X.; Vince, R. *Bioorg. Med. Chem.* **2006**, *14*, 2942. (b) Zhao, G.; Wang, C.; Liu, C.; Lou, H. *Mini-Rev. Med. Chem.* **2007**, *7*, 707.

(3) (a) Gelbard, H. A.; Maggirwar, S. B.; Dewhurst, S.; Schifitto, G. P. WO 2007076372, **2007**. (b) Mellman, I.; Jiang, A. WO 2007075911, **2007**.

(4) (a) Paolini, L. *Sci. Rep. Ist. Super. Sanita* **1961**, *1*, 86. (b) Okamoto, T.; Akase, T.; Izumi, S.; Inaba, S.; Yamamoto, H. JP 7220196, **1972**; *Chem. Abstr.* **1972**, *77*, 152142. (c) Winter, J.; Di Mola, N. DE 2442513, **1975**; *Chem. Abstr.* **1975**, *82*, 156255.

(5) (a) Stubbs, M. C.; Armstrong, S. A. *Curr. Drug Targets* **2007**, *8*, 703. (b) Shenoy, S.; Vasania, V. S.; Gopal, M.; Mehta, A. *Toxicol. Appl. Pharmacol.* **2007**, *222*, 80. (c) Seedhouse, C. H.; Hunter, H. M.; Lloyd-Lewis, B.; Massip, A.-M.; Pallis, M.; Carter, G. I.; Grundy, M.; Shang, S.; Russel, N. H. *Leukemia* **2006**, *20*, 2130.

(6) (a) Joseph, J.; Meijer, L.; Liger, F. FR 2876377, **2006**. (b) Das, S.; Brown, J. W.; Dong, Q.; Gong, X.; Kaldor, S. W.; Liu, Y.; Paraselli, B. R.; Scorah, N.; Stafford, J. A.; Wallace, M. B. WO 2007044779, **2007**.

(7) Fong, T. M.; Erondu, N. E.; Macneil, D. J.; Mcintyre, J. H.; Vander Pleog, L. H. T. WO 2004110368, **2004**.

(8) (a) Beccalli, E. M.; Clerici, F.; Marchesini, A. *Tetrahedron* **2001**, *57*, 4787. (b) Erba, E.; Gelmi, M. L.; Pocar, D. *Tetrahedron* **2000**, *56*, 9991. (c) Kaczmarek, L.; Peczynka-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkovska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 22457. (d) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vanderberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211. (e) Molina, P.; Alajarín, M.; Vidal, A.; Sánchez-Aranda, P. *J. Org. Chem.* **1992**, *57*, 929. (f) Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49. (g) Vera-Luque, P.; Alajarin, R.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 415.

(9) Majumder, S.; Bhuyan, P. J. *Synlett* **2011**, 173.

(10) Habib, P. M.; Rama, B. R.; Veerababurao, K.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron* **2009**, *65*, 5799.

(11) (a) Carini, D. J.; John, V. D.; Paul, E. A.; Andrew, T. C.; Alexander, L. J.; Michael, E. P.; William, A. P.; Joseph, B. S.; Gregory, J. W. *J. Med. Chem.* **1991**, *34*, 2525. (b) Koyama, M.; Ohtani, N.; Kai, F.; Moriguchi, I.; Inouye, S. *J. Med. Chem.* **1987**, *30*, 552. (c) Maxwell, J. R.; Wasdahl, D. A.; Wolfson, A. C. *J. Med. Chem.* **1984**, *27*, 1565.

(12) (a) Brown, M. US 3,338,915, **1967**; *Chem. Abstr.* **1968**, 87299. (b) Tarver, C. M.; Goodale, T. C.; Shaw, R.; Cowperthwaite, M. *Proc. Symp. Int. Detonation 6th* **1967**, 231; *Chem. Abstr.* **1980**, *92*, 8480. (c) Henry, R. A. US 3, 096, 312, **1963**.

(13) (a) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis, Tetrahedron Organic Chemistry Series*, Vol. 8; Pergamon Press: Oxford / UK, **1990**. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Carruthers, W.; Coldham, I. In *Modern Method of Organic Synthesis*; Cambridge University Press: Cambridge / UK, **2004**. (d) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(14) (a) Jung, M. E.; Yuk-Sun, L. P.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (b) Coldham, L.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(15) (a) Himo, F.; Demko, Z. P.; Noodleman, L. *J. Org. Chem.* **2003**, *68*, 9076. (b) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 12210. (c) Sutherland, D. R.; Tennant, G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 534. (d) Lauria, A.; Patella, C.; Diana, P.; Barraja, P.; Montalbano, A.; Cirrincione, G.; Dattolo, G.; Almerico, A. M. *Tetrahedron Lett.* **2006**, *47*, 2187.

(16) (a) Weber, L.; Illegen, K.; Almstetter, M. *Synlett* **1999**, 366. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Rev.* **1996**, *29*, 123. (c) Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Rev.* **1996**, *29*, 123.

(17) (a) Shestopalov, A. M.; Emeliyanova, Y. M.; Shestiopolov, A. A.; Rodinovskaya, I. A.; Niazimbetova, Z. I.; Evans, D. H. *Org. Lett.* **2002**, 423. (b) List, B.; Castello, C. *Synlett* **2001**, 1687. (c) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427. (d) Bagley, M. C.; Cale, J. W.; Bower, J. *Chem. Commun.* **2002**, 1682. (e) Cheng, J. F.; Chen, M.; Arthenius, T.; Nadzen, A. *Tetrahedron Lett.* **2002**, *43*, 6293. (f) Bertozzi, F.; Gustafsson, M.; Olsson, R. *Org. Lett.* **2002**, *4*, 3309. (g) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205.

(18) (a) Baruah, B.; Bhuyan, P. J. *Tetrahedron* **2009**, *65*, 7099. (b) Deb, M. L.; Majumder, S.; Baruah, B.; Bhuyan, P. J. *Synthesis* **2010**, 929. (c) Deb, M. L.; Bhuyan, P. J. *Synlett* **2008**, 325. (d) Deb, M. L.; Bhuyan, P. J. *Synthesis* **2008**, 2891.

(19) **General Procedure for Three-Component Reaction**
To a mixture of 1-Boc-2-chloro-3-formylindole (**3a**, 279 mg, 1 mmol), ethyl cyanoacetate (**4a**, 170 mg, 1.5 mmol), and NaN_3 (**5**, 80 mg, 1.24 mmol) in DMF (5 mL) were added 2 drops of H_2O. A catalytic amount (1–2 drops) of Et_3N was then added, and the reaction mixture allowed to stir for 3 h at 50–60 °C. After completion of the reaction, the mixture was cooled to r.t. and poured into H_2O with continuous stirring. A yellow-brownish solid product was formed after keeping the mixture inside the freezer overnight. Product **6a** was purified by preparative TLC using EtOAc–hexane (3:7).
Compound 6a
Yield 270 mg (71%); mp 221–223 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.07 Hz, 3 H), 1.72 (s, 9 H), 4.17–4.23 (m, 2 H), 7.20–7.86 (m, 3 H), 8.18 (s, 1 H), 8.57–8.63 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.23, 28.08, 62.20, 86.81, 105.09, 113.52, 115.22, 115.66, 121.09, 124.08, 124.40, 125.77, 130.83, 135.66, 146.37, 147.89,

162.57. MS (EI): *m/z* = 382.4 $[M + H]^+$. Anal. Calcd (%) for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 4.98; N, 18.37. Found: C, 59.65; H, 4.93; N, 18.42. IR ($CHCl_3$): ν_{max} = 2983.00, 2856.50, 1751.90, 1728.10 cm^{-1}. Similar compounds **6b**–**i** were synthesized and characterized.

(20) **Synthesis of Compound 3a**
Equimolar amounts of 2-chloro-3-formyl indole (**2**, 10 mmol, 1.79 g) and Boc-anhydride (10 mmol, 2.18 g) were stirred in the presence of catalytic amount of DMAP (0.12 g) and Et_3N (0.10 g) at 0–5 °C for 1 h using CH_2Cl_2 as solvent. The solvent was evaporated under reduced pressure, and the solid compound obtained was purified by column chromatography using PE–EtOAc (9:1) as eluent. The product **3** was obtained in 70% yield (1.20 g) as white crystalline compound; mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (s, 9 H), 7.26–7.40 (m, 2 H), 8.02–8.06 (m, 1 H), 8.27–8.30 (m, 1 H), 10.29 (s, 1 H).

Synthesis of Compound 3b
2-Chloro-3-formyl-indole (**2**, 1.78 g, 10 mmol) was taken in a round-bottom flask in DMF (10 mL) on magnetic stirrer. NaH (0.48 g, 20 mmol) was added into the mixture. When the temperature reached 0 °C, MeI (1.42 g, 10 mmol) was added gradually, and the reaction mixture allowed to stir for 1.5 h. An off-white solid formed which was almost pure product. Yield 1.59 g (82%); mp 79–80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 7.20–8.30 (m, 4 H), 10.12 (s, 1 H).

Synthesis of Compound 3c
2-Chloro-3-formyl-indole (**2**, 1.78 g, 10 mmol) was refluxed with allyl bromide(10 mmol) in the presence of K_2CO_3 (10 mmol) using acetone (10 mL) as solvent for 10 h to afford **3c**, 1.69 g (76%) as a colorless solid, mp 148–149 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80 (d, *J* = 11.4 Hz, 2 H), 5.10–5.27 (d, *J* = 10.2 Hz, 2 H), 5.95–6.07 (m, 1 H), 7.20–8.26 (m, 4 H), 10.16 (s, 1 H).

(21) **Synthesis of Compound [A]**
1-Boc-2-chloro-3-formylindole (**3a**, 558 mg, 2 mmol) was treated with ethyl cyanoacetate (**4a**, 283 mg, 2.5 mmol) in EtOH (8 mL). One drop of piperidine was added, and the reaction mixture was allowed to stir at r.t. for 30 min. The reaction mixture was kept inside the freezer overnight. The yellow solid which appeared in the reaction mixture was filtered, washed with cold EtOH and dried. Yield 508 mg (75%); mp 87–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, *J* = 3.6 Hz, 2 H), 1.72 (s, 9 H), 4.36–4.44 (m, 2 H), 7.20–8.10 (m, 4 H), 8.49 (s, 1 H).

(22) **Synthesis of α-Carboline 6a from [A]**
The condensed product [**A**] (339 mg, 1 mmol) was mixed with NaN_3 (**5**, 80 mg, 1.24 mmol) in DMF (5 mL) and 2 drops of H_2O were added. A catalytic amount (1–2 drops) of Et_3N was then added to the reaction mixture, and the whole was stirred for 3 h at 50–60 °C After completion of reaction, the mixture was cooled to r.t. and poured into H_2O with stirring. A yellow-brownish solid was formed after keeping the mixture inside the freezer overnight. Product **6a** was purified by preparative TLC using EtOAc–hexane (3:7); yield 251 mg (66%); mp 221–223 °C.

(23) Soledade, M.; Pedras, C.; Suchy, M.; Ahiahonu, W. K. *Org. Biomol. Chem.* **2006**, *4*, 691.