Synthesis of Indolo[3,2-*b*]carbazoles *via* an Anomeric-Based Oxidation Process: A Combined Experimental and Computational Strategy

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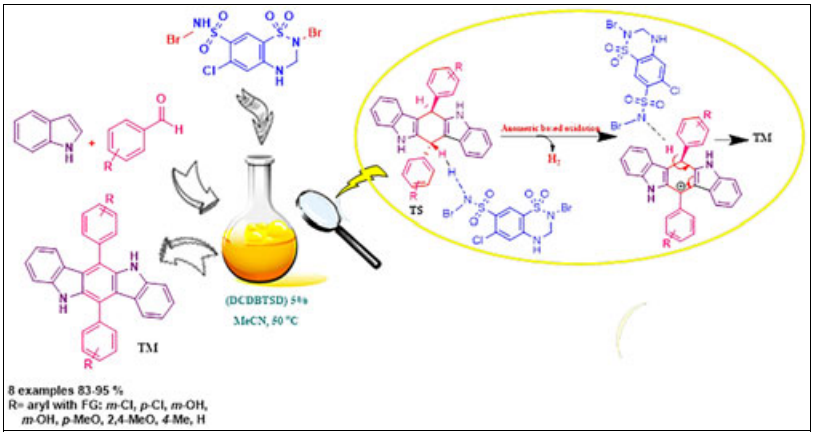

Indolo[3,2-b]carbazole is a molecule of great biological significance, as it is formed *in vivo* after consumption of cruciferous vegetables. The reaction of 1*H*-indole and various aldehydes in the presence of a catalytic amount of *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide as an efficient and homogeneous catalyst in acetonitrile at 50°C produces 6,12-disubstituted 5,7-dihydroindolo[2,3-*b*]carbazole with an in good to excellent yield. The presented technique offers a fast and robust method, by the use of inexpensive commercially available starting materials toward 6,12-disubstituted 5,7-dihydroindolo[2,3-*b*]carbazole. A new anomeric-based oxidation was kept in mind for the final step of the indolo[2,3-*b*]carbazoles synthesis. The suggested anomeric-based oxidation mechanism was supported by experimental and theoretical evidences.

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INTRODUCTION

Indolocarbazole derivatives (ICZs) are alkaloids exhibiting attractive biological properties such as antitumor and antibiotic activities [1,2]. Their strict and coplanar structural features give ICZs high HOMO levels and remarkable hole-transporting properties. Consequently, ICZs have been introduced as key electron-rich π-conjugated backbones in optoelectronic materials for applications such as organic field-effect transistor (OFET) [3–6] and organic light-emitting diode (OLED) [7–10]. Among of five likely isomers, 5,11-dihydroindolo[3,2-*b*]carbazole (referred to herein as indolo[3,2-*b*]carbazole or ICZ) has shown attractive structural and electrical properties (high charge carrier mobility) combined with good stability under atmospheric changes that makes them good components for use in organic electronics [11]. Numerous synthetic procedures for the synthesis of symmetrical and unsymmetrical indolo[3,2-*b*]carbazoles have been reported in the literature, most of which depend on multi-step sequences characterized by low overall yield [12–14]. A comprehensive overview of the synthesis and characterization of indolo[3,2-*b*]carbazoles can be found in the literature [1,11,15–17].

On the other hand, organic synthetic methodology, as rational designing philosophy for developing novel reagent systems for organic synthesis, continuously seeks for new reagents, best reaction conditions, and more efficient and selective methods. In this regard, a large group of compounds entitled *N*-halo reagents are widely used as catalysts and/or reagents in fine organic synthesis [18]. The *N*-halo derivatives include of amines, amides, imides, urea, saccharines, sulfonamides, and sulfonimides [18,19]. The synthesis and applications of *N*-halo reagents have been extensively reviewed in the literature [18–20], and the present work is a continuation of previous studies [21]

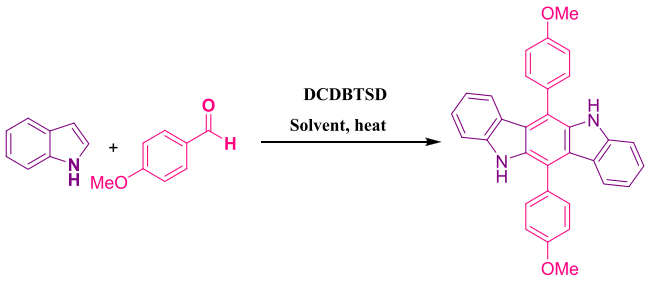


Figure 1. The presented model reaction in this study. [Color figure can be viewed at wileyonlinelibrary.com]

by the authors on the applications of *N*-halo reagents in organic synthesis. This study aims to prepare 5,11-dihydroindolo[3,2-*b*]carbazoles by using an *N*-bromo reagent via one-pot and anomeric based oxidation.

EXPERIMENTAL

Materials. All chemicals were purchased from Merck Company. The known products were identified by comparison of physical properties such as melting point and spectral data with those reported in the literature. Infrared spectroscopy was recorded on a Perkin Elmer GX FT-IR spectrometer using the KBr technique. Melting points were measured using a Büchi B-545 apparatus in open capillary tubes and are uncorrected. All reactions were monitored by thin-layer chromatography using silica gel SIL G/UV 254 plates.

Table 1

Optimization of conditions[a].

Entry	Solvent	Amount of catalyst/ mol%	Temp. (°C)	Time (min)	Yield[b] (%)
1	MeCN	-	50	180	-
2	MeCN	4	50	35	80
3	MeCN	5	50	15	96
4	MeCN	10	50	15	97
5	H_2O	5	50	180	26
6	CH_3CH_2OH	5	50	180	40
7	none	5	50	50	80
8	MeCN	5	40	50	80
9	MeCN	5	60	15	96

[a]Reaction conditions: 1*H*–indole (1 mmol), 4-methoxybenzaldehyde(1-mmol), solvent (2 mL), and DCDBTSD.
[b]Yields of isolated products.

Computational details. In this research, the computations were performed using the Gaussian 09 program [22]. Moreover, density functional theory has been used to investigate the reactions of intermediate VI in the presence of catalyst *N*,2-dibromo-6-chloro-3,4-dihydro-2*H*-benzo[e][1,2,4]thiadiazine-7-sulfonamide 1,1-dioxide (DCDBTSD). All geometry optimizations were performed at B3LYP/SVP level of the theory. The frequency calculations at the same level of the theory have also been performed to identify all of the stationary points as minima with no imaginary frequencies or transition structures with one imaginary frequency. In order to investigate the mechanism, the total electronic energy (E_{el} + ZPE) and the Gibbs-free energies have been used. The salvation energies (ΔG_{solv}) were calculated with the solvation model based on density (SMD) model using acetonitrile as a solvent. Then, the Gibbs-free energies in the solution were calculated by using equation $\Delta G_{(aq)} = \Delta G_{gas} + \Delta G_{solv}$. The intramolecular interactions were calculated on the basis of natural bond orbital [23] analyses.

General procedure for synthesis of DCDBTSD. A solution of sodium hydroxide (6 mol.L^{-1}, 1 mL) was added drop-wise to a round-bottomed flask (50 mL) containing hydrochlorothiazide (0.6 g, 2 mmol) in distilled water (2 mL) as it was being stirred for 10 min at room temperature. After the addition was complete, the reaction mixture was stirred for a further 20 min.

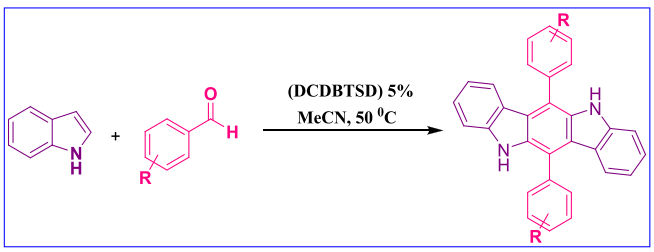


Figure 2. The synthesis of 6,12-disubstituted 5,7-dihydroindolo [3,2-b]carbazoles. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2

Synthesis of indolo[3,2-b]carbazoles in the presence of 5 mol% of DCDBTSD in acetonitrile at 50°C.

Entry	Ar	Time (min)	Yield (%)[a]	Mp. °C (lit.)[Ref]
1	C_6H_5	20	83	346–348 (350–352) [24]
2	4-ClC_6H_4	50	90	369–371 (364–366) [25]
3	2-OH C_6H_4	18	95	342–344(>300) [24]
4	4-MeO C_6H_4	15	90	378–380 (383–385) [24]
5	2,4-$(MeO)_2$ C_6H_4	15	93	400<
6	4-MeC_6H_4	20	91	400 < (400<) [24]
7	2-ClC_6H_4	50	92	338–340 (341–343) [24]
8	4-OHC_6H_4	20	95	400 < (400<) [24]

[a]Yields of isolated products.

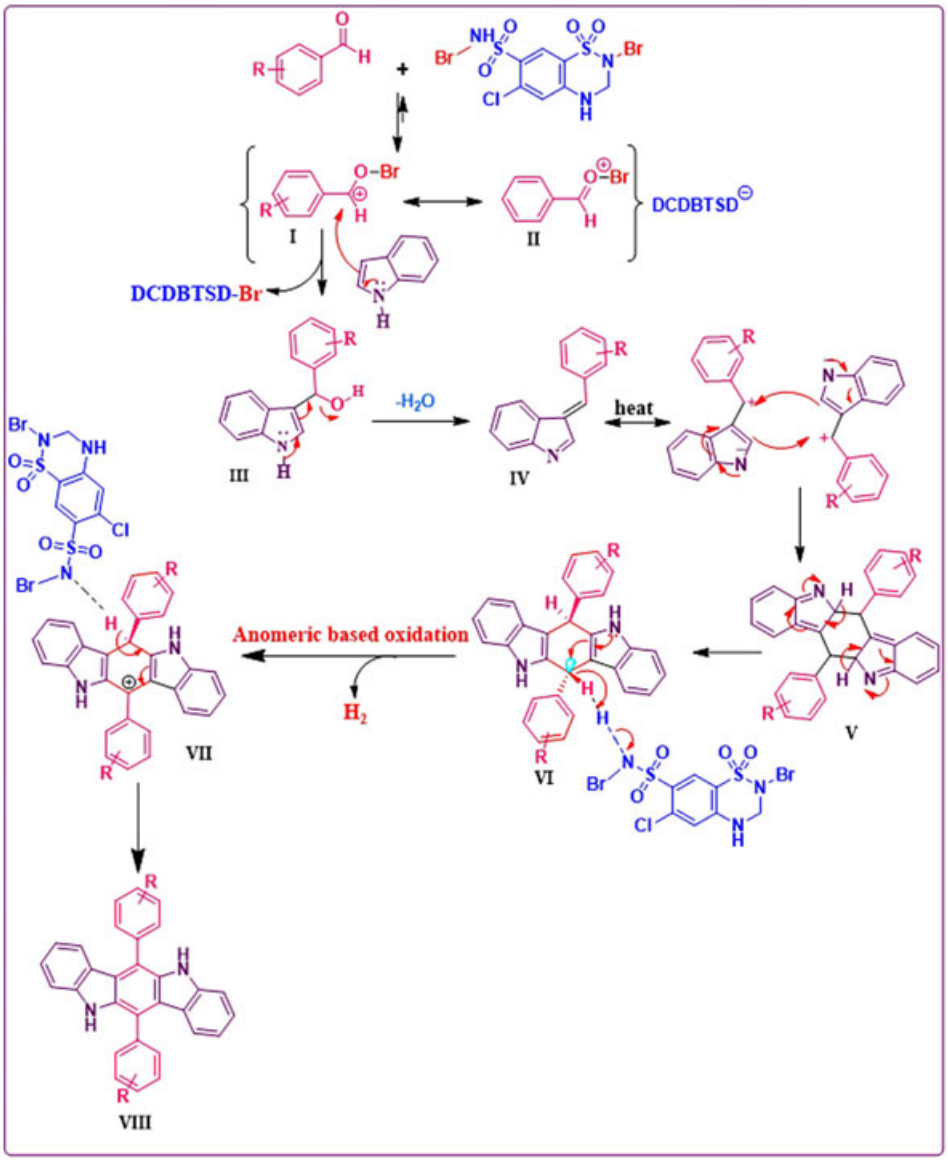


Figure 3. Suggested mechanism for the synthesis of indolo[3,2-b]carbazole derivatives. [Color figure can be viewed at wileyonlinelibrary.com]

Following this, bromine (0.08 mL, 3 mmol) was slowly added to the hydrochlorothiazide solution as it was being stirred for a period of 15 min at 0°C. The insoluble brominated catalyst was removed by filtration and washed with water (10 mL) to provide DCDBTSD at a yield of 90% (0.82 g) [19].

General procedure for the synthesis of indolo[3,2-b] carbazole derivatives. In the experimental method, the equimolar amounts of indole (2 mmol, 0.234 g), aldehyde (2 mmol), and DCDBTSD (0.0228 g, 5 mol%) were added to a round-bottomed 2flask containing MeCN (2 mL). The reaction mixture was stirred at 50°C for an appropriate time point as listed in Table 2. The desired solid product was obtained by simple filtration, dried, and recrystallized (DMF–$CHCl_3$).

RESULTS AND DISCUSSION

The initial studies were carried out one equimolar amounts of 1*H*–indole and 4-methoxybenzaldehyde in the presence of a catalytic amount of DCDBTSD as a model reaction (Fig. 1).

To determine the optimal reaction solvent, this reaction was examined in H_2O, CH_3CN, EtOH, and under solvent-free systems at 50°C. Table 1 indicates that the reaction using acetonitrile as a solvent resulted in a high yield and shorter reaction time (Table 1, entry 3).

The effect of the amount of catalyst was investigated through reactions carried out at DCDBTSD contents ranging from 4 to 10 mol%. It was found that an increase in the DCDBTSD content from 4, 5, to 10 mol% could increase the yield from 80% to 96% and 97%, respectively (Table 1, entries 2–4). It was found that 5 mol% of DCDBTSD in acetonitrile is satisfactory to catalyze the reaction (Table 1, entry 3). Notably, when this reaction was carried out in the absence of DCDBTSD, the yield of the product was very low (Table 1, entry 1). Several experiments were carried out at 40, 50, and 60°C in acetonitrile to determine the optimal temperature (Table 1, entries 3, 8, and 9). It was found that the most appropriate reaction temperature was 50°C (entry 3). In addition, the optimized conditions for the synthesis of 5,11-dihydroindolo[3,2-*b*]carbazoles have been depicted in Figure 2.

To delineate this method for library construction, the procedure was evaluated using various aromatic aldehydes (Table 2). The 6,12-disubstituted 5,7-dihydroindolo[3,2-b] carbazoles were selectively synthesized by condensation

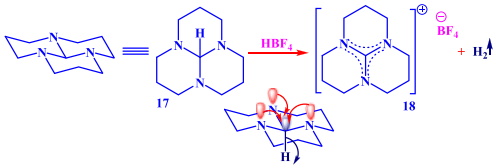


Figure 5. A striking example, which had been observed for an unusual hydride transfer from tricyclic orthoamide (16) through anomeric-based oxidation [27]. [Color figure can be viewed at wileyonlinelibrary.com]

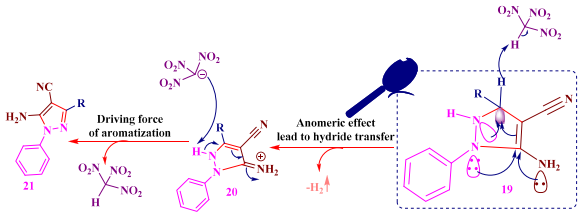


Figure 6. Synthesis of 1,4-dihydropyrano-[2,3-*c*]-pyrazole derivatives *via* anomeric-based oxidation [28]. [Color figure can be viewed at wileyonlinelibrary.com]

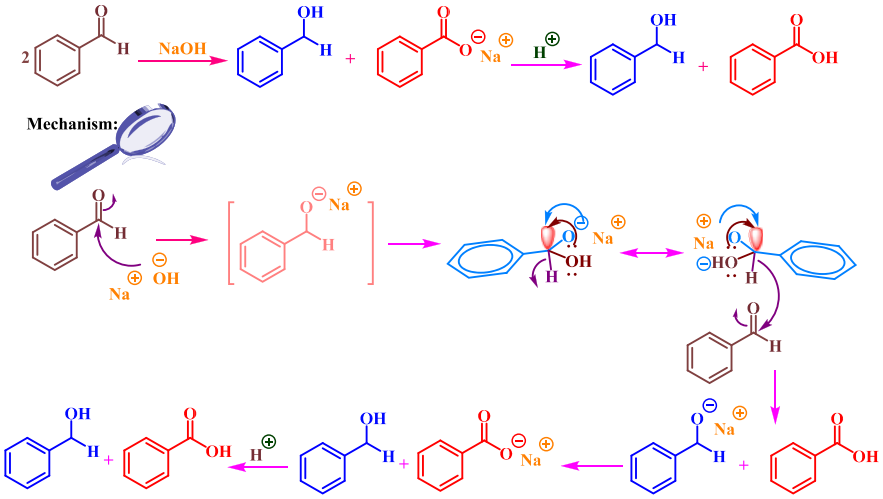


Figure 4. The proposed mechanism for the *in situ* oxidation–reduction in Cannizzaro reaction through unusual hydride transfer *via* anomeric-based oxidation [26]. [Color figure can be viewed at wileyonlinelibrary.com]

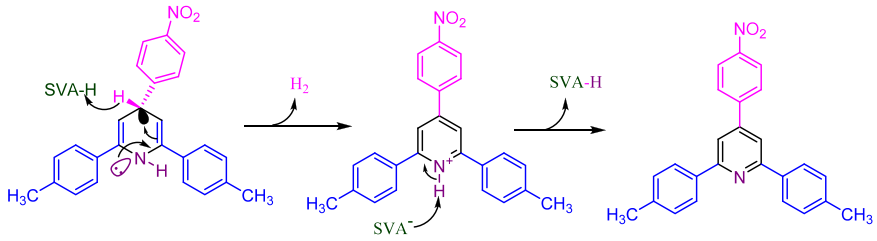


Figure 7. The synthesis of 2,4,6-triarylpyridines through anomeric-based oxidation [29]. [Color figure can be viewed at wileyonlinelibrary.com]

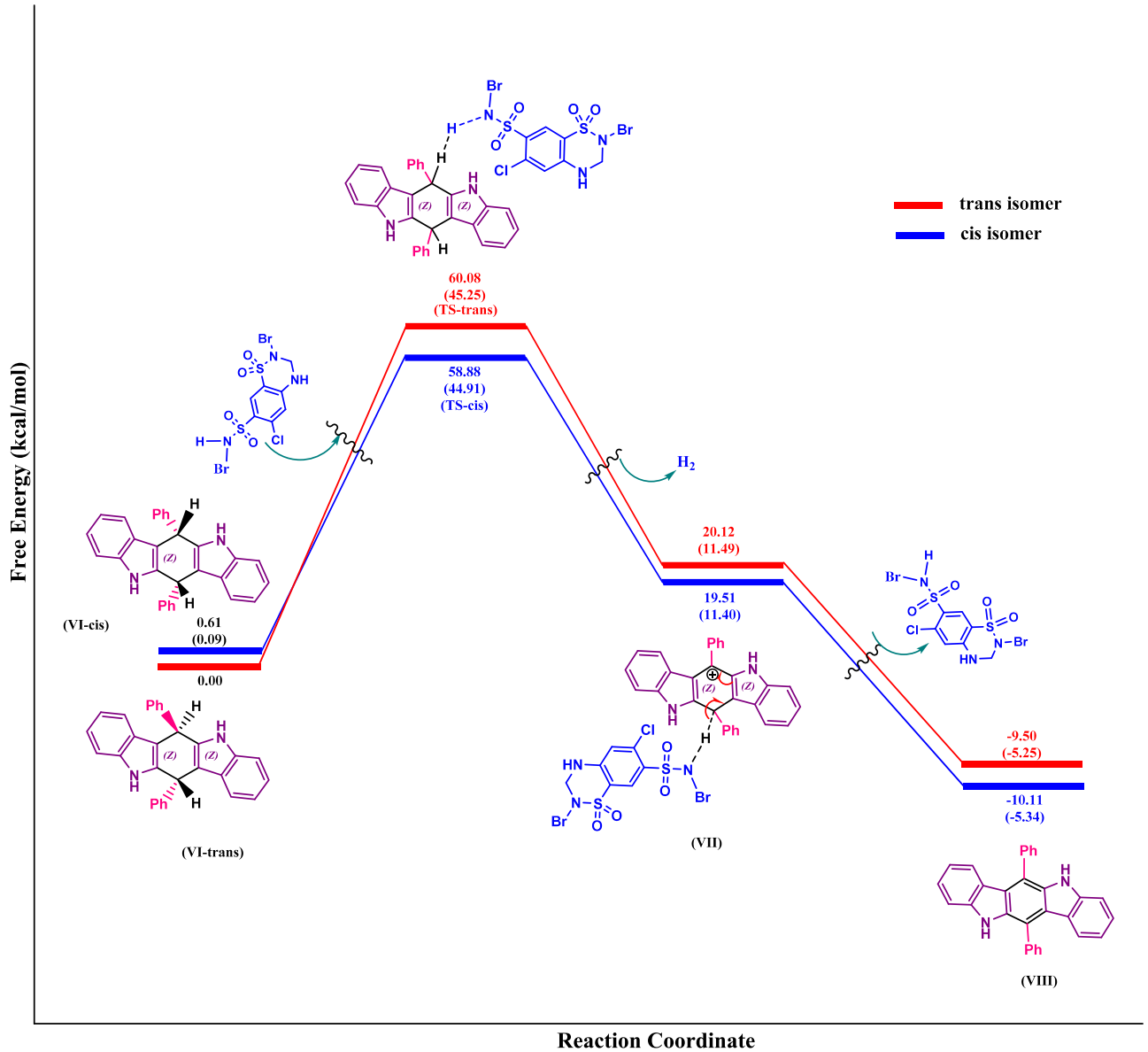


Figure 8. Energy profile calculated for synthesis of indolo[3,2-b]carbazole by catalyst DCDBTSD beginning from compound VI (see Fig. 3). The relative Gibbs-free energies in acetonitrile and the gas phase total electronic energies (E_{el} + ZPE, figures in parentheses) obtained from the B3LYP/SVP calculations both are given in kcal/mol. [Color figure can be viewed at wileyonlinelibrary.com]

of 1*H*-indole and aromatic aldehydes to produce excellent yields in the presence of 5 mol% of DCDBTSD in acetonitrile at 50°C.

It was noted that substituents in the aromatic ring of the aldehyde had a strong effect on the reaction. Electron-withdrawing groups in the aromatic ring of the aldehyde

decelerated that the reaction and the electron-donating groups accelerated the reaction. Because of the previously mentioned fact, it was not possible to synthesize indolo [3,2-*b*]carbazoles of 4-nitrobenzaldehyde.

Previously reported methods for the synthesis of indolo [3,2-b]carbazoles observed that indolo[2,3-b]carbazoles also formed during the reaction but were difficult to separate because of their insolubility [24]. In the present study, the indolo[2,3-b]carbazole isomer could not form, which makes this method more suitable for the synthesis of indolo[3,2- b]carbazoles. A plausible mechanism for the reaction is outlined in Figure 3.

It is likely that the described catalyst *in situ* release Br^+, which act as an electrophilic species that activates the aldehyde for an electrophilic attack of indole to generate intermediate III. Self-condensation occurs and results in the formation of tetrahydro intermediate VI. Earlier reports suggest aerobic auto-oxidation of tetrahydro compound VI to its corresponding indolo[3,2-b]carbazole. In contrast to the previously reported mechanistic explanation for the final step of the previously described organic synthesis [24,25], we believed that this step might progress by uncommon hydride transfer as well as Cannizzaro reaction (Fig. 4) [26] and H_2 releasing from tricyclic orthoamide (Fig. 5) [27]. Recently, we suggested an anomeric-based oxidation (ABO) for the final step for the synthesis of 1,4-dihydropyrano-[2,3-*c*]-pyrazole [28] and 2,4,6-triarylpyridine derivatives synthesis [29] (Figs 6 and 7). For approving of this aim, reaction was carried out under nitrogen atmosphere and in the absence of any molecular oxygen. We observed that the reaction progressed in the absence of any oxygen molecules and under atmosphere of nitrogen. The previously mentioned evidence shows that the conversion of intermediate VI to its corresponding indolo[3,2-b]carbazoles VIII (Fig. 8) might happen via unusual hydride transfer and releasing of molecular hydrogen (H_2). The C─H bond is so weaken *via* electron donation from the C─C double bond into the anti-bonding of C─H (σ^*_{C-H} orbital), which it can be broken *via* reaction with a proton to afford molecular hydrogen. Very recently, we introduced a new term for this phenomena entitled "anomeric-based oxidation." The major reason of ABO is the driving force of aromatization, which will be supported via stereoelectronic and/or anomeric effect.

To investigate the final step in mechanistic process for the synthesis of indolo[3,2-b]carbazole density functional theory has been used. Starting from VI, two different orientations of Ph substituents and C─H groups on intermediate VI with respect to each other give cis and trans isomers. As illustrated in Figure 1, by addition of catalyst DCDBTSD, intermediate VII will be formed through the formation of transition structures, TS-cis and TS-trans, and then removing the molecular hydrogen (H_2). According to the

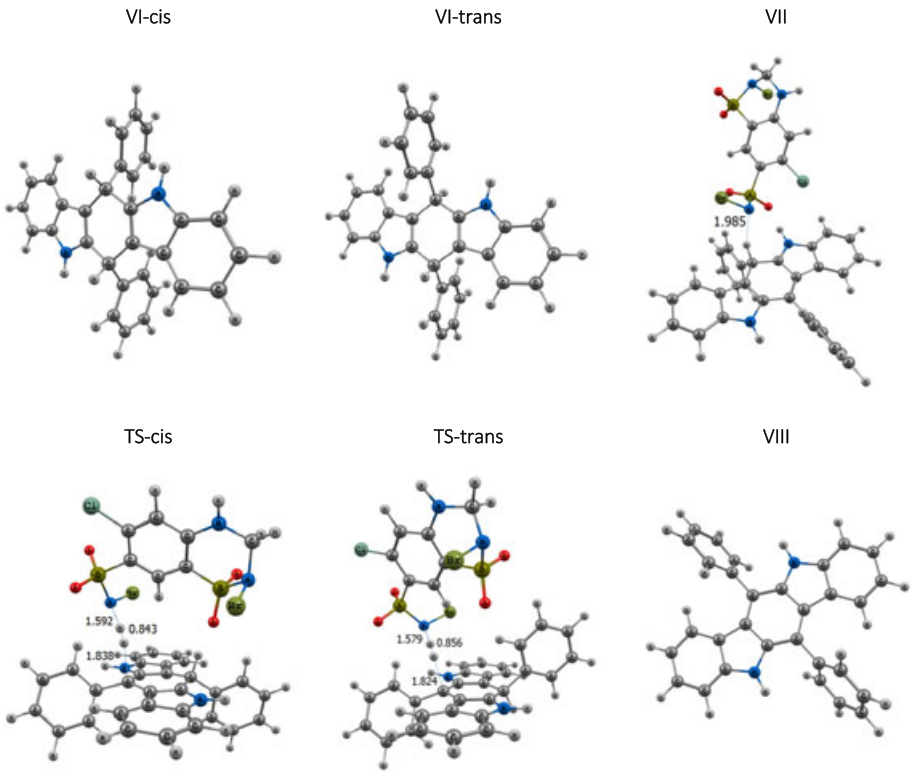
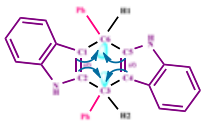


Figure 9. The optimized structure of all compounds involved in conversion of VI to VIII according to the mechanism suggested in Figure 8. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3

The main second order perturbation energies (kcal/mol) calculated for intermediate **VI**.

Donor–acceptor interactions	Isomers of intermediate VI	
	Cis	Trans
π C1-C2 →σ* C6-H1	2.83	2.88
π C1-C2 →σ* C3-H2	3.36	3.23
π C4-C5 →σ* C6-H1	3.36	3.23
π C4-C5 →σ* C3-H2	2.83	2.88
Total	12.38	12.22



values of calculated Gibbs-free energies in acetonitrile solution, this reaction is about 20.1 and 19.5 kcal/mol endothermic for cis and trans isomers, respectively.

In the final step of the reaction, intermediate VII converts into indolo[3,2-b]carbazole (VIII) through an exothermic process ($\Delta G = -29.62$ kcal/mol for both cis and trans isomers). In conclusion, the process of conversion of VI to VIII through the releasing molecular hydrogen is exothermic ($\Delta G = -9.50$ and -10.11 kcal/mol for cis and trans isomers, respectively).

The important step of ABO is the direct elimination of H_2 molecule from intermediate VI and catalyst DCDBTSD (Fig. 9) in which the C─H bond in intermediate VI is so weakened because of the delocalization of π electron of C─C double bonds to σ* C─H bonds. The natural bond orbital analysis of donor–acceptor interactions, which are shown in Table 3, identified the previous delocalization for cis and trans isomers of intermediates VI are 12.38 and 12.22 kcal/mol, respectively.

Thus, the previous theoretical studies support our suggested mechanism and show that the releasing molecular hydrogen (H_2) is quite possible in such systems. The optimized structures of all compounds involved in our suggested mechanism are shown in Figure 2. The Cartesian atomic coordinates of all compounds involved in our suggested mechanism are available in the Supporting Information.

CONCLUSIONS

In conclusion, the described method demonstrates a novel and efficient method for the synthesis of indolo [3,2-b]carbazole derivatives catalyzed effectively by DCDBTSD. A new mechanistic approach is proposed for the final step of the indolo[3,2-b]carbazole synthesis. In addition to the experimental efforts, the theoretical study has also supported the ABO in the final step of the mechanistic pathway. It is speculated that the proposed mechanism have a high potential for entering into the graduate text books in the future.

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REFERENCES AND NOTES

[1] Janosik, T.; Wahlström, N.; Bergman, J. Tetrahedron 2008, 64, 9159.
[2] Chao, W. R.; Yean, D.; Amin, K.; Green, C.; Jong, L. J Med Chem 2007, 50, 3412.
[3] Wakim, S.; Bouchard, J.; Simard, M.; Drolet, N.; Tao, Y.; Leclerc, M. Chem Mater 2004, 16, 4386.
[4] Zhao, G.; Dong, H.; Zhao, H.; Jiang, L.; Zhang, X.; Tan, J.; Meng, Q.; Hu, W. J Mater Chem 2012, 22, 4409.
[5] Jiang, H.; Zhao, H.; Zhang, K. K.; Chen, X.; Kloc, C.; Hu, W. Adv Mater 2011, 23, 5075.
[6] Boudreault, P. L. T.; Wakim, S.; Blouin, N.; Simard, M.; Tessier, C.; Tao, Y.; Leclerc, M. J Am Chem Soc 2007, 129, 9125.
[7] Ting, H. C.; Chen, Y. M.; You, H. W.; Hung, W. Y.; Lin, S. H.; Chaskar, A.; Chou, S. H.; Chi, Y.; Liu, R. H.; Wong, K. T. J Mater Chem 2012, 22, 8399.
[8] Lengvinaite, S.; Grazulevicius, J.; Grigalevicius, S.; Gu, R.; Dehaen, W.; Jankauskas, V.; Zhang, B.; Xie, Z. Dyes Pigm 2010, 85, 183.
[9] Hu, N. X.; Xie, S.; Popovic, Z. D.; Ong, B.; Hor, A. M. Synth Met 2000, 111, 421.
[10] Su, J. Y.; Lo, C. Y.; Tsai, C. H.; Chen, C. H.; Chou, S. H.; Liu, S. H.; Chou, P. T.; Wong, K. T. Org Lett 2014, 16, 3176.
[11] Van Snick, S.; Dehaen, W. Org Biomol Chem 2012, 10, 79.
[12] Ishii, H.; Sakurada, E.; Murakami, K.; Takase, S.; Tanaka, H. Perkin Trans 1988, 1, 2387.
[13] Lehmann, J.; Hartmann, U. Arch Pharm 1989, 322, 451.
[14] Katritzky, A. R.; Li, J.; Stevens, C. V. J Org Chem 1995, 60, 3401.
[15] Gu, R.; Hameurlaine, A.; Dehaen, W. Synlett 2006, 1535.
[16] Wakim, S.; Aïch, B. R.; Tao, Y.; Leclerc, M. Polym Rev 2008, 48, 432.
[17] Bergman, J.; Janosik, T.; Wahlström, N. Adv Heterocycl Chem 2001, 80, 1.
[18] Veisi, H.; Ghorbani-Vaghei, R.; Zolfigol, M. A. Org Prep Proced Int 2011, 43, 489.
[19] Kolvari, E.; Ghorbani-Choghamarani, A.; Salehi, P.; Shirini, F.; Zolfigol, M. J Iran Chem Soc 2007, 4, 126.
[20] Kolvari, E.; Koukabi, N.; Khoramabadi-zad, A.; Shiri, A.; Ali Zolfigol, M. Curr Org Synth 2013, 10, 837.
[21] Khazaei, A.; Zolfigol, M. A.; Karimitabar, F.; Nikokar, I.; Moosavi-Zare, A. R. RSC Adv 2015, 5, 71402.
[22] Frisch, M.; Trucks, G.; Schlegel, H. B.; Scuseria, G.; Robb, M.; Cheeseman, J.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. e.; Gaussian, Inc. Wallingford, CT, 2009.
[23] Glendening, E.; Reed, A.; Carpenter, J.; Weinhold, F. NBO, version 3.1. 1998.
[24] Deb, M. L.; Majumder, S.; Baruah, B.; Bhuyan, P. J Synthesis 2010, 929.
[25] Black, D. S.; Ivory, A. J.; Kumar, N. Tetrahedron 1995, 51, 11801.
[26] Zolfigol, M. A.; Gholami, H.; Khakyzadeh, V. Principle of organic synthesis with a new approach; Bu-Ali Sina University Publishers: Hamedan, 2014.

[27] Erhardt, J. M.; Wuest, J. D. J Am Chem Soc 1980, 102, 6363.
[28] Zolfigol, M. A.; Afsharnadery, F.; Baghery, S.; Salehzadeh, S.; Maleki, F. RSC Adv 2015, 5, 75555.
[29] Zolfigol, M. A.; Safaiee, M.; Afsharnadery, F.; Bahrami-Nejad, N.; Baghery, S.; Salehzadeh, S.; Maleki, F. RSC Adv 2015, 5, 100546.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.