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Copper-mediated rapid and facile oxidative dehydrogenation of dihydrobenzocarbazoles

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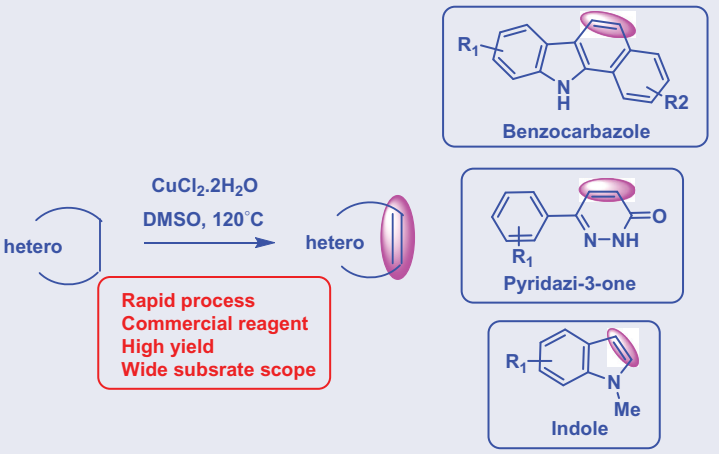
ABSTRACT

Rapid method for the oxidative dehydrogenation of dihydrobenzocarbazoles has been introduced by using bench scale and commercially available reagent; copper chloride, in excellent yield with easy workup. The scope of the reaction has been studied with broad range of substitutes

GRAPHICAL ABSTRACT



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Benzocarbazole; copper chloride; dehydrogenation; heterocyclic compound

Introduction

Dehydrogenation is an important process in organic synthesis for the industrial and academic persistence. Myriad of work has been focused for the development of dehydrogenation process, including metal-promoted process is known to be a key step.[1] Over the last few decades, copper-mediated reactions such as cylication,[2a] oxidation,[2b] coupling reaction[2c–g] and one-pot addition[2h] received considerable attention in organic synthesis. Moreover, copper (II) salt plays a significant role in organic transformations. Literature survey revealed that Cu (II)/O_2 in presence of chelex,[3a] propyl framed-ligand[3b] and HPPDO[3c] used for oxidation. Additionally, (a) cylization: Cu(II)/O_2/TEMPO,[3d] (b) epoxidation: Cu(II)/O_2 with aldehyde as co-oxidant or

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norbornene,[3e] (c) addition reaction: Cu(II)/O_2 in acidic condition,[3f] (d) coupling reaction: Cu(II)/methanol, pyridine was successfully used.[3g] Copper chloride is become a favorite choice owing to their inexpensive, nontoxic, environmentally benign characteristics and insensitive to air as well as moisture. The main advantage is that it can be easily removed from the reaction by aqueous workup. Additionally, copper chloride gives a high degree of regioselectivity with less possibility of side products. However, literature survey shows that a very limited number of heterocyclic moieties undergo dehydrogenation process by copper chloride while required extra additives and oxidants.[4a–e]

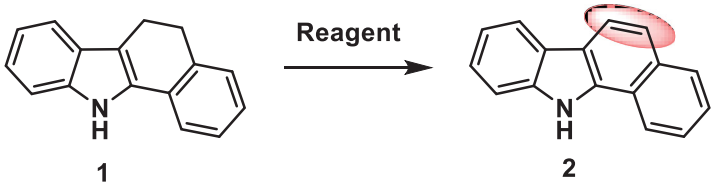
Due to notable significance of benzo[*a*],[*b*],and[*c*]-carbazoles in material and biological activity, huge efforts have been made for their construction.[5] Various synthetic approaches such as metal-catalyzed,[6a–e,6h–i] domino annulation of indoles,[6f] and tandem cyclization/C − H functionalization of two different alkynes[6g] has been reported. However, Fischer–Borsche synthesis is the most common practical method used for the preparation of benzocarbazoles. In general, this involves the condensation of phenylhydrazine with α or β-tetralone, followed by aromatization. The final step, aromatization of dihydrobenzo[*a*]carbazole, is the most challenging task. To the best of our knowledge, very few reagents are documented in the literature to afford aromatization process. Following limitations have been observed in the aromatic process; (a) Pd/C is often used with high boiling point solvent,[7a,b] (b) DDQ, an organic-derived reagent is used,[7c,d] and (c) transition metal-based transformations are used for the preparation of benzocarbazoles.[7e] However, these approaches required high temperature, loading of stoichiometric amounts of catalyst, longer reaction time and low yield. To the best of our knowledge, a very few reports are documented in the literature for the dehydrogenation of dihydrobenzocarbazoles. Therefore, development of rapid, efficient and conventional method for dehydrogenation of dihydrobenzocarbazoles is exceedingly desirable.

Result and discussions

We started our experimental strategy by condensation of commercially available phenyl hydrazine with tetralone which was readily converted into dihydrobenzo[*a*]carbazole. Encouraged from our previous report based on the development of regioselective one-pot dehydrogenation and iodination of dihydrobenzocarbazole using periodic acid in PEG-400.[8] In this process, iodo-benzo[*a*]carbazole product was achieved by using two-fold of periodic acid as a reagent. Recently, we developed copper-mediated organic transformation for biological active scaffold.[9] Therefore, we thought commercially available copper-source could be used for dehydrogenation of dihydrobenzocarbazoles.

Initially, when reaction was performed in the presence of CuCl, CuO and $CuSO_4$ in dimethyl sulphoxide (DMSO) at 100 °C for 2 h, did not afford the desired product (Table 1, entry a, b, c). Trace amount of product was observed by using $Cu(OAc)_2$ while moderate yield was obtained by $CuBr_2$. Recently, Guo et al. exposed the copper (I)-catalyzed synthesis of 2-arylquinolines under aerobic oxidative protocol.[10] To employ the similar reaction condition (CuCl/O_2 in DMSO at 120 °C for 10 h), desired product was obtained in moderate yield.

Table 1. Optimization condition.



Entry	Reagent[a] (eqv)	Time (min)	Yield[b] (%)
a	CuCl (2 eqv)[c]	120	NR
b	CuO (2 eqv)	120	NR
c	$CuSO_4.5H_2O$ (2 eqv)	120	NR
d	$Cu(OAc)_2$ (2 eqv)	120	trace
e	$CuBr_2$ (2 eqv)	120	40[d]
f	$CuCl_2.2H_2O$ (0.1 eqv)[c]	120	20[d]
g	$CuCl_2.2H_2O$ (0.5 eqv)	120	42[d]
h	$CuCl_2.2H_2O$ (1 eqv)	35	81
i	$CuCl_2.2H_2O$ (2 eqv)	10	89
j	$CuCl_2.2H_2O$ (3 eqv)	10	88

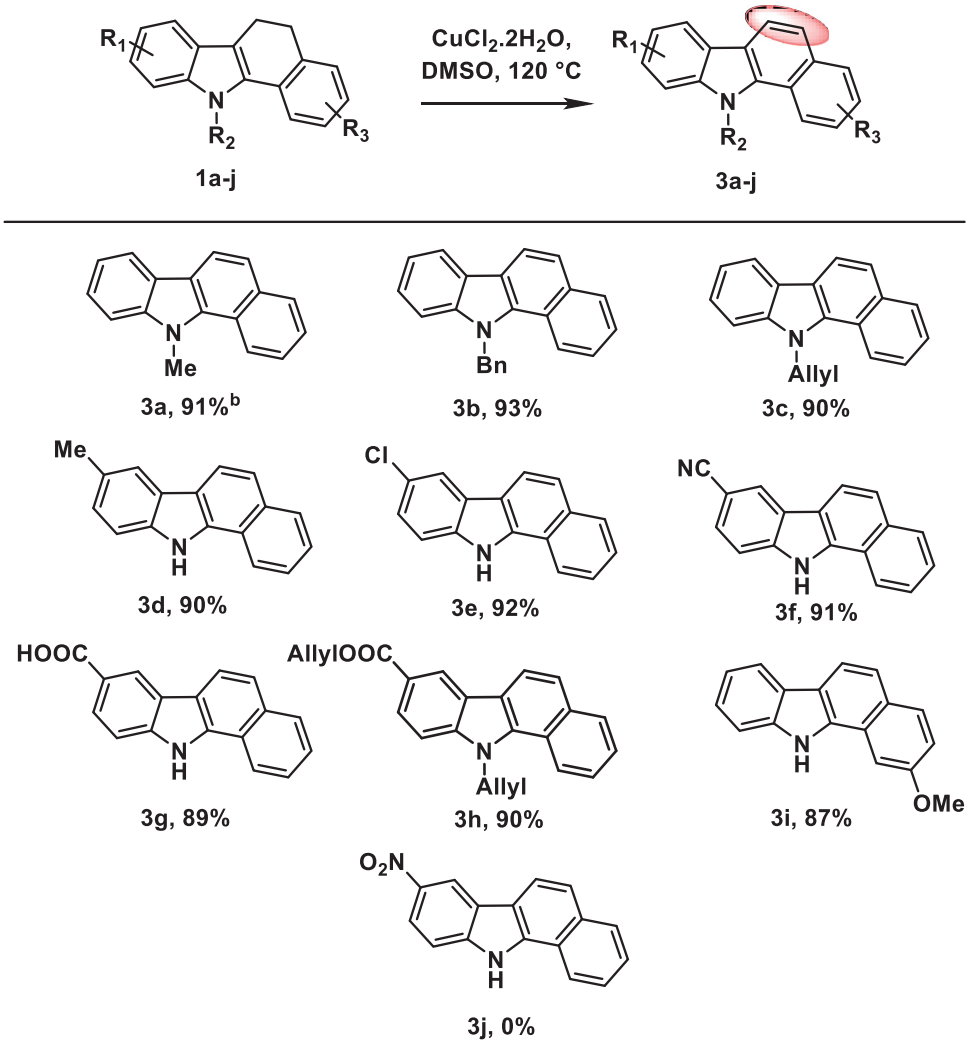
[a]All reagents have good solubility in DMSO.
[b]Isolated yield.
[c]Reagent was used with O_2.
[d]Product was isolated with recovering of starting substrate.

Further, we optimized the reaction condition with copper chloride as reagent. On increasing the mole% of copper chloride from 10 mol% to equimolar proportional (Table 1, entry f–h), the yield was increases with moderate to good yield. Under the oxygen atmosphere with 10 mol% $CuCl_2{\cdot}2H_2O$ in dimethyl sulphoxide at 120 °C for 2 h, no significant change of yield was observed. To increase the two-fold degree of the $CuCl_2{\cdot}2H_2O$ afforded the desired dehydrogenated product in 10 min with good yield (Table 1, entry i). Finally, attempts to increase the reaction temperature and proportional of copper chloride does not affect the yield of the product.

To make the generality of this new method and check the versatility of copper-catalyzed dehydrogenation, various substituents of dihydrobenzocarbazoles were successful studied (Scheme 1, entry **3a–j**). Notably, no effect of electron-donating and electron-drawing substitutes were observed in oxidative dehydrogenation process. Significantly, *N*-allyl group remains intact throughout the whole procedure (Scheme 1, entry **3h**). However, **3j** could not supported the optimized condition. This may be due to interactive property of copper chloride with nitro-functionality.

After exploring the reactivity pattern of various dihydrobenzo[*a*]carbazoles, we further planned to explore the scope of this process to other *N*-heterocycles such as dihydropyridazine-3-one and indoline. Dehydrogenation of **4a–f** under optimized condition proceeded smoothly, afforded product **5a–f** in good yield. The reaction was neat and clean (Scheme 2).

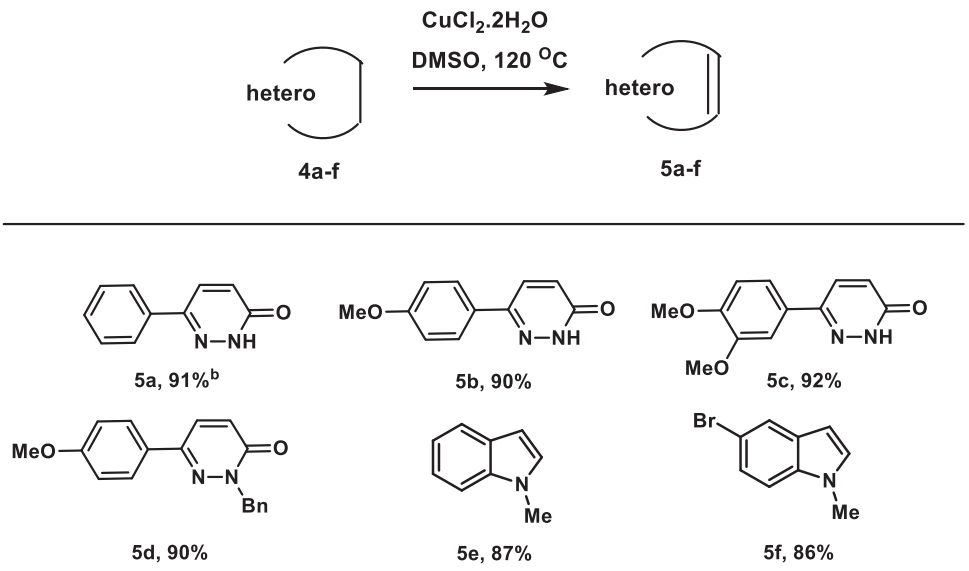
To study the insight of mechanism for copper-mediated oxidative dehydrogenation process, we studied the formation of copper chloride-substrate **1** complex. In order to understand the copper chloride-substrate **1** complex formation, we performed an experiment in which copper chloride was thoroughly grid with substrate **1** from room temperature to 100 °C for 30 min. The progress of reaction was monitored by tlc and IR spectra after the interval of 10 min (Fig. 1). The IR spectra A and B attributed that



Scheme 1. Rapid oxidative dehydrogenation of dihydrobenzocarbazole using copper chloride. [a]Reaction condition: Substrate **1** (2.2 mmol), $CuCl_2.2H_2O$ (4.5 mmol) in DMSO at 120 °C for 30 min. [b]Isolated yield.

region 3431–3167 cm^{-1} shows a broad band due to N-H streaching. Quagliano et al. have found that formation of nitrogen to metal bond results in a broading of N–H stretching frequency.[11] Clearly, this indicates that copper chloride first undergo the process of complex formation with substrate **1** while the aliphatic region 2941 cm^{-1}, 2883 cm^{-1} and 2833 cm^{-1} remain intact. However, the appearance of strong intense band at 1595 cm^{-1} and increase of aromatic C–H band from 3049 cm^{-1} to 3051 cm^{-1} resembles the progress of dehydrogenation process. The additional characteristic bands are obtained at 1325 cm^{-1}, 1307 cm^{-1}, and 1280 cm^{-1}.

On the other hand, we tested optimized reaction under aerobic and inert condition. Molecular oxygen is an ultimate oxidant that has been attracted much attention from the synthetic community.[12] To our delight, when oxygen gas was bubbled in reaction mixture, the dehydrogenation process was accomplished in a short time (10 min). While



Scheme 2. Rapid oxidative dehydrogenation of other heterocycles using copper chloride. [a]Reaction condition: Substrate 1 (2.2 mmol), $CuCl_2.2H_2O$ (4.5 mmol) in DMSO at 120 °C for 10 min. [b]Isolated yield.

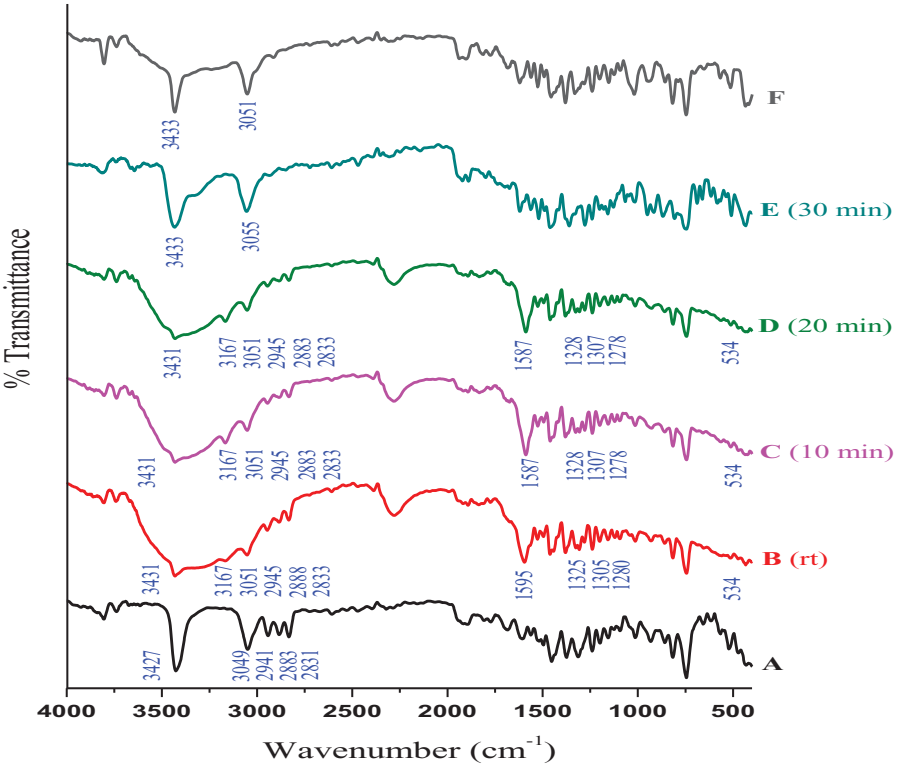
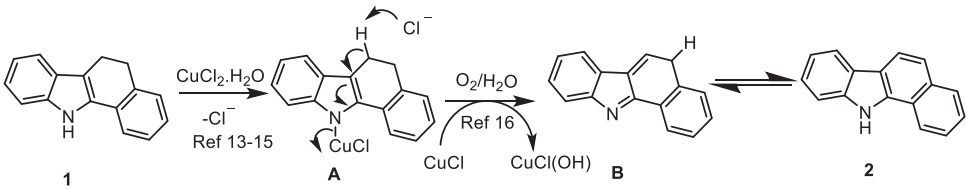
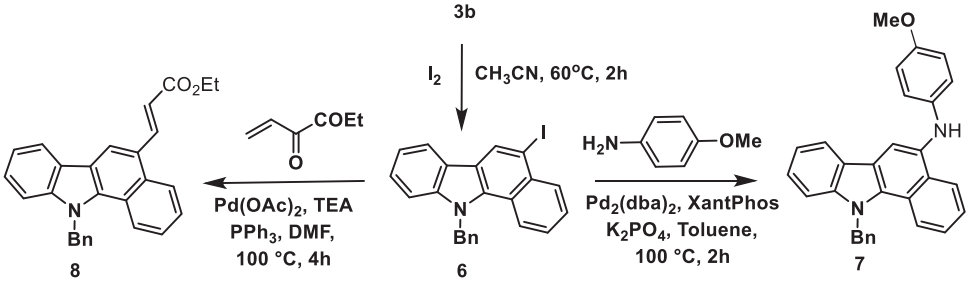


Figure 1. FTIR Study of complex formation (A) substrate 1; (B) copper chloride/substrate 1 grinding at rt; (C) copper chloride/substrate 1 grinding at 100 °C for 10 min; (D) copper chloride/substrate 1 grinding at 100 °C for 20 min; (E) copper chloride/substrate 1 grinding at 100 °C for 30 min; (F) Product 2.



Scheme 3. Plausible mechanism for aromatization of dihydrobenzo[*a*]carbazole.



Scheme 4. Utility of copper-mediated hydrogenation process for coupling reaction.

rate of reaction was slow under nitrogen and argon atmosphere. This study showed molecular oxygen is the necessary condition for dehydrogenation process.

Based on these results, plausible reaction mechanism of oxidative dehydrogenation process is outlined in Scheme 3. Copper (II) chloride preferably interact with substrate **1** in DMSO to give the complex **A**.[13,14] However, copper (II) chloride have good solubility in DMSO. White et al.[15]explained the reactivity of series of copper (II) salt based on its anion counterpart, leading to intermediate **A**. In the next step, elimination of CuCl furnished intermediate **B**. Under the aerobic condition, CuCl could get converted into CuCl(OH) (Scheme 3).[16] Finally, the intermediate **B** could isomerized to product **2.**

To foresee the utility of the present method, the requisite dehydrogenated product **3b** was treated with iodine in acetonitrile at 60 °C. The Buchward coupling reaction with benzyl protected iodo substituted benzo[*a*]carbazole **(6)** and aniline has been carried in presence of $Pd_2(dba)_2$, Xanthphos, K_2PO_4, toluene at 100 °C for 2 h. Similarly, Heck coupling was performed with **6** and ethyl acrylate under $Pd(OAc)_2$, triethylamine, toluene at 100 °C for 4 h, afforded the corresponding product in 69% yield (Scheme 4). This preparation could allow the development of various promising precursors for material sciences.

Experimental

General procedure for the synthesis of benzocarbazole, pyridazine-3-one and indole

In 50 ml round bottom flask, $CuCl_2{\cdot}2H_2O$ (4.5 mmol) thoroughly dissolved in 10 mL DMSO. To this solution, dihydrobenzo[*a*]carbazole (2.2 mmol) was added and stirred

for 30 min at room temperature. The resulting mixture was heated at 120 °C through open vessel. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched by few drops of con. HCl and poured in ice cold water. The product was isolated. Filter and recrystalized by methanol.

11*H*-benzo[*a*]carbazole (3a): Yield 91%, m.p.: 230–231 °C, IR (ν cm^{-1}): 3030, 1600, 1587; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, $J = 8.1$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.45–7.28 (m, 7H), 4.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.4, 136.5, 134.8, 133.5, 130.1, 125.5, 125.2, 123.9, 123.8, 121.1, 120.6, 120.1, 119.7, 118.9, 119.1, 111.0, 44.6; HRMS (ES) $m/z = 232.1004$ calcd for $C_{17}H_{13}N$ $[M+H]^+$, found 232.1007

Representative procedure for the 5-Iodo-11N-benzyl-benzo[a]carbazole (6)

In round bottom flask, 11 *N*-Benzyl-benzo[*a*]carbazole (0.912 mmol) and iodine (1.368 mmol) in acetonitrile (5 mL) was stirred for 2 h at 60 °C. The progress of the reaction was checked by TLC. The workup of the reaction was carried out in ice cold saturated sodium thiosulfate solution (20 mL). Extracted wih ethyl acetate and washed with water followed by brine solution (50 mL × 2) and further purified by column chromatography (ethyl acetate: pet-ether) to give the desired product.

Yield: 90%; m.p.: 156–160 °C; IR (cm^{-1}): 3053, 1218; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.81 (d, $J = 1.6$ Hz, 1H), 8.39 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 7.77 (t, $J = 6.8$ Hz, 1H), 7.65–7.55 (m, 3H), 7.28–7.22 (m, 4H), 7.04 (d, $J = 6.8$ Hz, 2H), 6.17 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 140.31, 137.79, 135.29, 134.05, 133.48, 132.70, 131.46, 129.37,129.37, 129.11, 127.79, 127.46, 127.13, 126.17, 126.17, 124.29, 123.42, 122.64, 119.88, 113.06, 90.18, 84.42, 49.22.

Representative procedure for the Buckward coupling (7)

A mixture of *N*-benzyl-iodo-benzo[a]carbazole (0.115 mmol), $Pd_2(dba)_3$ tri(dibenzylideneacetone)dipalladium (15 mol%), Xanthphos (30 mol%) and K_3PO_4 (0.168 mmol) in dry toluene was added 4-methoxy aniline (0.138 mmol) under the flow of argon and immediately seal the pressure tube. Reaction mixture was stirred at 80 °C for 2 h. The completion of the reaction was confirmed by TLC. The reaction mixture was extracted by ethyl acetate and wash the organic layer with ammonium chloride and water. Evaporate organic solvent under vacuum and purified by column chromatography using ethyl aceate:hexane.

Yield: 79%; m.p.: 309–312 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.48–8.38 (m, 1H), 8.30–8.24 (m, 1H), 8.17 (d, $J = 7.8$ Hz, 1H), 8.09 (s, 1H), 7.70 (d, $J = 8.6$ Hz, 2H), 7.52–7.38 (m, 3H), 7.34 − 7.18 (m, $J = 21.3$, 7.1 Hz, 4H), 7.13 (d, $J = 7.3$ Hz, 2H), 6.83 (q, $J = 9.1$ Hz, 4H), 6.15 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.55, 141.43, 141.10, 138.35, 133.92, 131.44, 129.46, 129.43, 129.29, 127.63, 126.33, 126.14, 125.58, 125.11, 124.84, 122.98, 122.84, 120.14, 120.11, 119.21, 117.41, 115.12, 111.68, 110.22, 55.70, 49.13.

Representative procedure for the Heck coupling (8)

A mixture of N-benzyl-iodo-benzo[a]carbazole (0.115 mmol), ethyl acrylate (0.173 mmol), triphenyl phosphine (20 mol%), triethylamine Et_3N (2 equiv), and palladium acetate $Pd(OAc)_2$ (5 mol%) in dimethyl formamide sealed in pressure tube under argon atmosphere. Reaction mixture was stirred at 100 °C temperature for 5 h. The completion of the reaction was confirmed by TLC. The reaction mixture was extracted by ethyl acetate and wash with ammonium chloride and water. Evaporate organic solvent under vacuum and purified by column chromatography using ethyl aceate:hexane.

Yield: 81%; m.p.: 311–317 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.56 (d, $J = 15.6$ Hz, 1H), 8.44 (d, $J = 8.0$ Hz, 2H), 8.32 (d, $J = 8.2$ Hz, 1H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.59 (t, 1H), 7.50 (t, $J = 7.7$ Hz, 3H), 7.37 (t, $J = 7.4$ Hz, 1H), 7.31 − 7.18 (m, $J = 24.3$, 7.1 Hz, 4H), 7.09 (d, $J = 7.5$ Hz, 2H), 6.85 (d, $J = 15.6$ Hz, 1H), 6.14 (s, 2H), 4.28 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.0, 142.1, 141.5, 137.9, 136.2, 131.3, 129.1, 127.6, 126.2, 126.2, 126.1, 124.5, 123.3, 123.2, 123.0, 121.9, 121.0, 120.6, 120.1, 119.1, 118.5, 110.5, 60.1, 49.2, 14.6.

Conclusion

In conclusion, we have developed a rapid and efficient protocol of dehydrogenation process for variety of dihydrobenzocarbazole using copper chloride. Further, this method is extended to different *N*-heterocylic compounds. The advantages of this method are shorter reaction time, no column chromatography and have a wide substrate scope with excellent yield. The present method is found to be expedient and elegant. Further studies toward broadening the scope to include related heterocycles and applications are underway.

Acknowledgements

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