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A FACILE SYNTHESIS OF INDOLO[2,3-*b*]CARBAZOLES FROM THE REACTION OF DI(2-INDOLYL)METHANE AND AROMATIC ALDEHYDES CATALYZED BY OXALIC ACID

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Abstract – Oxalic acid catalyzed condensation of di(2-indolyl)methane with aromatic aldehydes has been established. Various indolo[2,3-*b*]carbazole derivatives were prepared in good isolated yields (up to 94.5%). Compared with literature methods, the present protocol features mild reaction conditions, easily controlled selectivity, good functional group tolerance, and simple operation procedures.

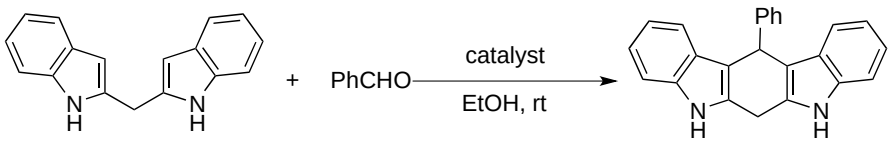
In recent years indole derivatives have received considerable attention because of their remarkable biological and pharmacological activities.[1] Various indole derivatives, such as indolocarbazole alkaloids have been reported as versatile intermediates for the synthesis of drugs and display a range of biological, pharmacological and medicinal activities.[2] Among the various indolocarbazoles, the indolo[3,2-*b*]carbazoles not only have been widely applied as organic electronic materials, such as blue luminescent materials and p-channel semiconductors, but also importantly as anion sensors and liquid crystals.[3] Obviously, the indolo[3,2-*b*]carbazoles play an important role in a variety of aspects. However, the application of the indolo[2,3-*b*]carbazoles remains potentially restricted due to the lack of efficient synthetic strategies.[4] A direct method for the synthesis of indolo[3,2-*b*]carbazoles involves the condensation with aliphatic or aromatic aldehydes catalyzed by protic or Lewis acids, but failed to give the indolo[2,3-*b*]carbazoles.[5] Recently, Deb et al. reported the synthesis of dihydroindolo[2,3-*b*]carbazole from an I_2-catalyzed reaction of 1*H*-indole and aldehydes, the results showed that the challenge of the regioselectivity of the condensation reaction was solved, but the reaction required high temperature and the 6,12-position of the products were certainly disubstituted by alkyl or acyl.[6] Subsequently, Su et al. reported a new synthetic strategy for indolo[2,3-*b*]carbazole *via* a double intramolecular Buchwald−Hartwig reaction.[4] In the same year, EI Sayed succeeded to synthesize the novel tetrahydroindolo[2,3-*b*]carbazoles *via* electrophilic condensation reactions of bisindolylmethanes (BIMs)

with ketones or aldehydes.[7] Furthermore, Xiao described a synthesis of unsymmetrical bisindolylmethanes featuring a catalyst-free procedure as well as Rao featuring silica gel-catalyst.[8] However, these new methods have a number of disadvantages, e.g. drastic conditions, a tedious workup procedure, poor yields of the desired products and multistep procedures. Therefore, the exploration of an inexpensive, nontoxic and readily available methods under mild conditions is of great significance.

In principle, the 3-position of indole is the preferred site for the electrophilic substitution reactions.[9] But the previous methods for the synthesis of indolo[2,3-*b*]carbazole derivatives involve the condensation of bisindolylalkanes with electrophiles (aldehydes or ketones or imines) that the 3-position of indole was substituted, thus the 2-position of indole is not easily reacted for electrophilic substitution reactions. In this work, a new synthetic strategy has been established for the efficient synthesis of indolo[2,3-*b*]carbazoles, which were obtained through the condensation of di(2-indolyl)methane with aromatic aldehydes, and this process is simple and green, with broad substrate scope and good functional group tolerance.

Initially, we examined the model reaction of benzaldehyde with di(2-indolyl)methane[10] in ethanol under room temperature in the presence of different catalysts. As shown in Table 1, the reaction did not proceed in the absence of any catalysts. And among the scanned catalysts (2 mol%), AcOH, $ZnCl_2$ and $AlCl_3$, failed to afford the desired compound (Table 1, entries 7-9).

Table 1. The effect of different catalysts for condensation of di(2-indolyl)methane with benzaldehyde[a]



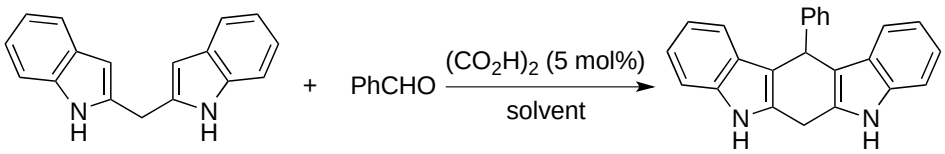
Entry	Catalyst	Amount of catalyst (mol%)	Yield/%[b]
1	-	-	0
2	*p*-TsOH	2	18.5
3	HCl	2	12.2
4	H_2SO_4	2	8.0
5	$(CO_2H)_2$	2	45.2
6	$(CO_2H)_2$	5	94.5
7	AcOH	2	0
8	$ZnCl_2$	2	0
9	$AlCl_3$	2	0

[a] Benzaldehyde: 1.0 mmol; di(2-indolyl)methane: 1.0 mmol; EtOH: 2 mL, rt, 5 h. [b] Isolated yield.

Other catalysts, including *p*-TsOH, HCl, H_2SO_4, promoted the reaction successfully, but the yields of indolo[2,3-*b*]carbazole were lower, 18.5%, 12.2% and 8.0%, respectively (Table 1, entries 2-4). Delightedly, in the course of the study it was foundthat only $(CO_2H)_2$ gave the desired product in 45.2% yield (Table 1, entry 5), and we further found that 94.5% yield of indolo[2,3-*b*]carbazole was obtained when 5 mol% of the catalyst was used (Table 1, entry 6). It is noteworthy that the catalytic process has no other by-products and is easy to separate.

Then, the solvent effect on the condensation of di(2-indolyl)methane with benzaldehyde was also investigated, and the results were collected in Table 2. The solvent was found to have significant effect on the yield of product. We conducted the first work in water, but the reaction did not occur (Table 2, entry 1). The same result appeared, when the reaction was carried out in *n*-BuOH, DMF, THF, toluene (Table 2, entries 6, 8-10). Excitedly, the catalyst system showed the excellent performance in MeOH, EtOH, MeCN. Particularly, the reaction proceeded smoothly in EtOH and an isolated yield of 94.5% was achieved at room temperature (Table 2, entry 3). So EtOH was considered to be optimal solvent for further study.

Table 2. Optimizing conditions for the condensation of di(2-indolyl)methane with benzaldehyde[a]



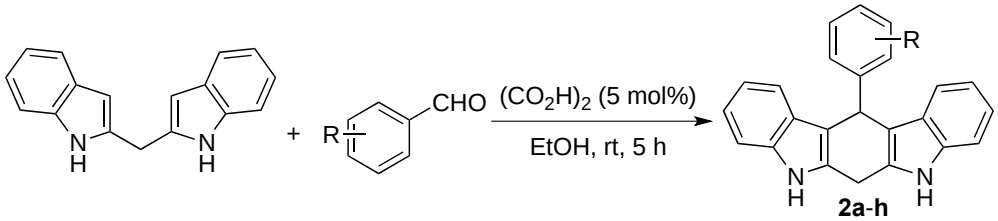
Entry	Solvent	Temperature/°C	Time/h	Yield/%[b]
1	H_2O	rt	5	0
2	MeOH	rt	5	63.7
3	EtOH	rt	5	94.5
4	EtOH	rt	3	62.3
5	EtOH	60	1.5	68.5
6	*n*-BuOH	rt	5	0
7	MeCN	rt	5	53.5
8	DMF	rt	5	0
9	THF	rt	5	0
10	toluene	rt	5	0

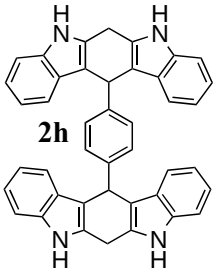
[a] Benzaldehyde: 1.0 mmol; di(2-indolyl)methane: 1.0 mmol; solvent: 2 mL.
[b] Isolated yield.

Under the optimized reaction conditions, we set out to investigate the scope initially, thus focusing on aromatic aldehydes. The results were summarized in Table 3. As can be seen, substrates bearing either electron-donating or electron-withdrawing substituents on the phenyl ring showed excellent reactivity.

However, the electron-donating substituents on the phenyl ring obtained higher yields of the isolated products, compared to the electron-withdrawing substituents, and the best yield can be up to 94.5% (Table 3, entries 1-6). On the other hand, the -OMe at the 2-position of aromatic aldehyde decreased the yield of the corresponding product (**2g**) due to the steric hindrance. Interestingly, terephthalaldehyde was well tolerated, and multi-indolo[2,3-*b*]carbazole (**2h**) was isolated in 80% yield (Table 3, entry 8).

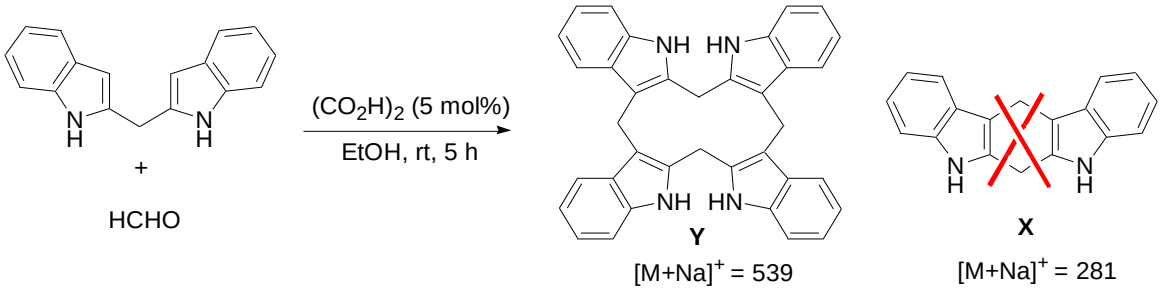
Table 3. Oxalic acid-catalyzed condensation of di(2-indolyl)methane with aromatic aldehydes[a]



Entry	R	Product	Yield/%[b]
1	H	**2a**	94.5
2	*p*-Me	**2b**	94
3	*p*-OMe	**2c**	93.7
4	*p*-NMe_2	**2d**	91
5	*p*-F	**2e**	90
6	*p*-Br	**2f**	91
7	*o*-OMe	**2g**	85
8[c]	*p*-CHO	**2h** 	80

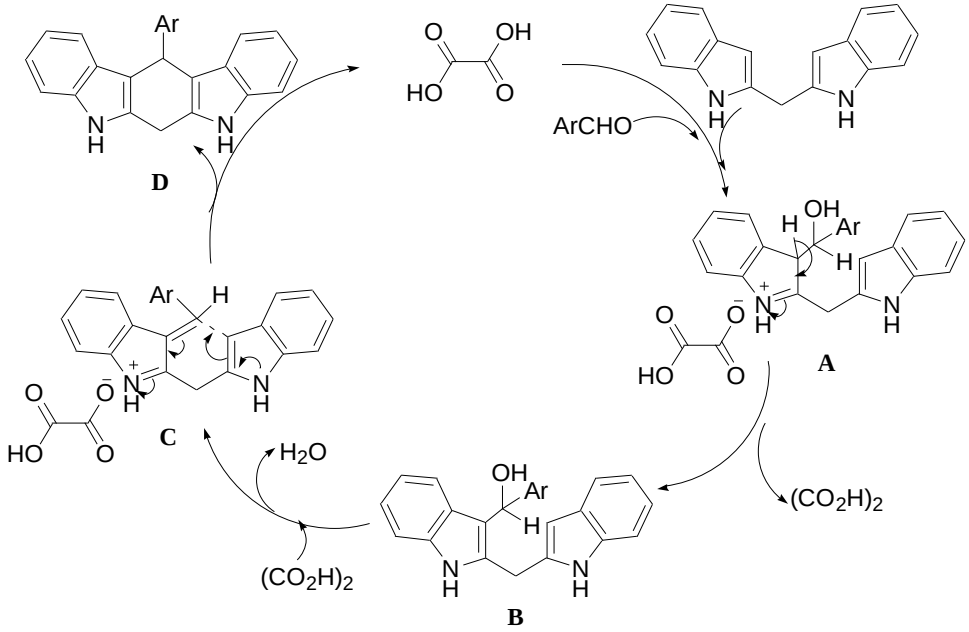
[a] Aldehyde: 1.0 mmol; di(2-indolyl)methane: 1.0 mmol; EtOH: 2 mL; rt, 5 h. [b] Isolated yield. [c] 4,4-diacetylbiphenyl: 0.5 mmol; di(2-indolyl)methane: 1.0 mmol.

Furthermore, the reaction of aliphatic aldehydes and di(2-indolyl)methane were carried out under the optimized conditions. However, the reaction was poor and no desired compounds were produced. To our surprise, when the reaction of formaldehyde and di(2-indolyl)methane was carried out, the indole derivative **Y** ($[M+Na]^+$ = 539) was detected by mass spectral analysis, but the expected indolo[2,3-*b*]carbazole **X** ($[M+Na]^+$ = 281) was not detected at all, which indicated that the condensation of formaldehyde and di(2-indolyl)methane probably occured intermolecularly (Scheme 1).



Scheme 1. Oxalic acid-catalyzed condensation of di(2-indolyl)methane with formaldehyde

On the basis of the knowledge of experimental results and the previous reports,[11] a possible mechanism for oxalic acid catalyzed formation of indolo[2,3-*b*]carbazole from di(2-indolyl)methane and aldehyde is proposed (Scheme 2). The initial step of the mechanism is that a molecule of di(2-indolyl)methane directly attacks aromatic aldehyde activated by oxalic acid to produce intermediate **A** *via* electrophilic substitution reaction. Accompanying with leaving of oxalic acid, the intermediate **B** is formed. Then, the oxalic acid activates **B**, and intermediate **C** is generated after loss of a molecule of H_2O. Meanwhile, the electrophilic reaction occurs intramolecularly at the intermediate **C**. With a molecule oxalic acid released, the indolo[2,3-*b*]carbazole **D** is finally produced.



Scheme 2. Plausible mechanism

In summary, a strategy for using oxalic acid as an efficient catalyst for electrophilic substitution reactions of di(2-indolyl)methane with aromatic aldehydes has been developed, which gives structurally diverse indolo[2,3-*b*]carbazoles with yields up to 94.5%. The mild reaction conditions and simple offset process

render this methodology a practical protocol. Further investigation on other applications of these type indolo[2,3-*b*]carbazoles is on the way in our laboratory.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II-400 MHz with reference to TMS as the internal standard and DMSO-d_6 as the solvent. Mass spectra were recorded with an AMD40223 (Interambulacra) spectrometer.

Starting Materials. Di(2-indolyl)methane was prepared by previously reported procedures.[10] All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Products (2a-g).

12-Phenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2a). All synthetic processes were performed in argon atmosphere. To a solution of di(2-indolyl)methane (1 mmol) in EtOH (2 mL) were added aldehyde (1 mmol) and oxalic acid (0.05 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, and a lot of solid was precipitated. Upon completion, the reaction mixture was filtered and the filtrate was washed with cold EtOH (5 mL) to give **2a** (317 mg, 94.5%); a white solid; mp 246-248 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 2H), 7.36 (d, *J* = 2.0 Hz, 2H), 7.31 (d, *J* = 4.0 Hz, 2H), 7.16-7.20 (m, 4H), 7.04-7.08 (m, 1H), 6.95-6.99 (m, 2H), 6.79-6.83 (m, 2H), 5.47 (s, 1H), 4.18-4.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.81, 137.03, 131.72, 128.79, 128.46, 126.65, 126.16, 120.85, 118.69, 118.65, 112.34, 111.26, 39.05, 23.28; HRMS (ESI): [M+H$^+$] calcd. for $[C_{24}H_{19}N_2]^+$, 335.1548; found, 335.1557.

12-*p*-Tolyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2b): a white solid; mp 231-233 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.05 (s, 2H), 7.30 (d, *J* = 4.0 Hz, 2H), 7.23 (d, *J* = 4.0 Hz, 2H), 7.17 (d, *J* = 4.0 Hz, 2H), 6.95-6.99 (m, 4H), 6.79-6.83 (m, 2H), 5.42 (s, 1H), 4.16-4.41 (m, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.78, 137.02, 134.92, 131.63, 129.06, 128.65, 126.67, 120.82, 118.76, 118.61, 112.46, 111.23, 38.63, 23.27, 21.10; HRMS (ESI): [M+H$^+$] calcd. for $[C_{25}H_{21}N_2]^+$, 349.1705; found,349.1701.

12-(4-Methoxyphenyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2c): a white solid; mp 260-262 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.04 (s, 2H), 7.31 (d, *J* = 4.0 Hz, 2H), 7.25 (d, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 4.0 Hz, 2H), 6.96-7.00 (m, 2H), 6.80-6.84 (m, 2H), 6.74 (d, *J* = 4.0 Hz, 2H), 5.42 (s, 1H), 4.16-4.40 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.62, 138.73, 137.04, 131.56, 129.61, 126.69, 120.79, 118.76, 118.59, 113.77, 112.59, 111.21, 55.26, 38.18, 23.26; HRMS (ESI): [M+H$^+$] calcd. for $[C_{25}H_{21}N_2O]^+$, 365.1654; found, 365.1660.

12-(4-Dimethylaminophenyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2d): a light yellow solid; mp 285-287 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (s, 2H), 7.30 (d, *J* = 4.0 Hz, 2H), 7.20 (d,

J = 4.0 Hz, 2H), 7.14 (d, *J* = 4.0 Hz, 2H), 6.95-6.99 (m, 2H), 6.79-6.83 (m, 2H), 6.55 (d, *J* = 4.0 Hz, 2H), 5.34 (s, 1H), 4.15-4.39 (m, 2H), 2.78 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.98, 137.05, 134.51, 131.43, 129.17, 126.83, 120.74, 118.94, 118.54, 112.96, 112.69, 111.17, 40.74, 38.11, 23.31; HRMS (ESI): [M+H$^+$] calcd. for $[C_{26}H_{24}N_3]^+$, 378.1970; found, 378.1968.

12-(4-Fluorophenyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2e): a white solid; mp 225-227 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.10 (s, 2H), 7.37-7.40 (m, 2H), 7.32 (d, *J* = 4.0 Hz, 2H), 7.17 (d, *J* = 4.0 Hz, 2H), 6.97-7.02 (m, 2H), 6.81-6.85 (m, 2H), 5.49 (s, 1H), 4.17-4.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 142.94, 137.04, 131.74, 130.45, 126.54, 120.92, 118.73, 118.60, 115.22, 115.01, 112.17, 111.32, 38.16, 23.24; HRMS (ESI): [M+H$^+$] calcd. for $[C_{24}H_{18}FN_2]^+$, 353.1454; found, 353.1454.

12-(4-Bromophenyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2f): a white solid; mp 237-239 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.12 (s, 2H), 7.37 (d, *J* = 4.0 Hz, 2H), 7.31-7.34 (m, 4H), 7.17 (d, *J* = 4.0 Hz, 2H), 6.97-7.01 (m, 2H), 6.82-6.86 (m, 2H), 5.49 (s, 1H), 4.18-4.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.40, 137.07, 131.91, 131.40, 131.07, 126.51, 121.02, 119.07, 118.84, 118.57, 111.84, 111.40, 38.37, 23.26; HRMS (ESI): [M+H$^+$] calcd. for $[C_{24}H_{18}BrN_2]^+$, 413.0653; found, 413.0640.

12-(2-Methoxyphenyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazole (2g): a white solid; mp 266-268 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.02 (s, 2H), 7.30 (d, *J* = 4.0 Hz, 2H), 7.10-7.13 (m, 3H), 7.01-7.05 (m, 1H), 6.95-6.99 (m, 2H), 6.79-6.83 (m, 2H), 6.66 (d, *J* = 4.0 Hz, 1H), 6.54-6.58 (m, *J* = 4.0 Hz, 1H), 5.98 (s, 1H), 4.17-4.42 (m, 2H), 4.12 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.61, 136.95, 134.46, 131.88, 129.98, 127.07, 126.57, 120.92, 120.83, 118.66, 118.55, 118.38, 112.77, 111.18, 56.34, 39.36, 23.25; HRMS (ESI): [M+H$^+$] calcd. for $[C_{25}H_{21}N_2O]^+$, 365.1654; found, 365.1658.

Procedure for the Preparation of Products (2h). All synthetic processes were performed in argon atmosphere. To a solution of di(2-indolyl)methane (1 mmol) in EtOH (2 mL) were added 4,4-diacetylbiphenyl (0.5 mmol) and oxalic acid (0.05 mmol) at room temperature. The mixture was stirred at room temperature for 5 h, and a lot of solid was precipitated. Upon completion, the reaction mixture was filtered and the filtrate was washed with cold EtOH (5 mL) to give **2h** (236 mg, 80%); a white solid; mp >300 °C (EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.92 (s, 4H), 7.19 (d, *J* = 2.0 Hz, 4H), 7.13 (s, 4H), 6.93 (d, *J* = 4.0 Hz, 4H), 6.84-6.88 (m, 4H), 6.61-6.65 (m, 4H), 5.29 (s, 2H), 4.06-4.25 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.72, 137.08, 131.59, 128.82, 126.89, 120.76, 118.97, 118.53, 112.31, 111.18, 39.27, 23.32; HRMS (ESI): [M+H$^+$] calcd. for $[C_{42}H_{31}N_4]^+$, 591.2549; found, 591.2548.

Procedure for the Reaction of Di(2-indolyl)methane and Formaldehyde: To a solution of di(2-indolyl)methane (1 mmol) in EtOH (2 mL) were added formaldehyde (1 mmol) and oxalic acid (0.05

mmol) at room temperature. The mixture was stirred at room temperature for 5 h and a white solid was precipitated. Then the mixture was filtered and the white solid was detected by mass spectral analysis. MS[M+Na^+] calcd. for $[C_{36}H_{28}N_4Na]^+$, 539.22; found, 539.32.

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REFERENCES

1. H.-J. Knölker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303; M. Prudhomme, *Eur. J. Med. Chem.*, 2003, **38**, 123.
2. T. Janosik, N. Wahlström, and J. Bergman, *Tetrahedron*, 2008, **64**, 9159; W.-R. Chao, D. Yean, K. Amin, C. Green, and L. Jong, *J. Med. Chem.*, 2007, **50**, 3412; C. Bailly, X. G. Qu, J. B. Chaires, P. Colson, C. Houssier, M. Ohkubo, S. Nishimura, and T. Yoshinari, *J. Med. Chem.*, 1999, **42**, 2927; M. Facompre, J.-F. Goossens, and C. Bailly, *Biochem. Pharmacol.*, 2001, **61**, 299.
3. N.-X. Hu, S. Xie, Z. Popovic, B. Ong, and A.-M. Hor, *J. Am. Chem. Soc.*, 1999, **121**, 5097; T. Tsuchimoto, H. Matsubayashi, M. Kaneko, Y. Nagase, T. Miyamura, and E. Shirakawa, *J. Am. Chem. Soc.*, 2008, **130**, 15823; P.-L. T. Boudreault, S. Wakim, N. Blouin, M. Simard, C. Tessier, Y. Tao, and M. Leclerc, *J. Am. Chem. Soc.*, 2007, **129**, 9125; B. Gómez-Lor, B. Alonso, A. Omenat, and J. L. Serrano, *Chem. Commun.*, 2006, 5012.
4. J.-Y. Su, C.-Y. Lo, C.-H. Tsai, C.-H. Chen, S.-H. Chou, S.-H. Liu, P.-T. Chou, and K.-T. Wong, *Org. Lett.*, 2014, **16**, 3176.
5. H. V. Dobeneck and I. Maas, *Chem. Ber.*, 1954, **87**, 455; J. Bergman, S. Högberg, and J.-O. Lindström, *Tetrahedron*, 1970, **26**, 3347.
6. M. L. Deb, B. Baruah, and P. J. Bhuyan, *Synthesis*, 2008, 286.
7. M. T. EI Sayed, K. M. Ahmed, K. Mahmoud, and A. Hilgeroth, *Eur. J. Med. Chem.*, 2015, **90**, 845; M. T. EI Sayed, K. Mahmoud, A. Hilgeroth, and I. M. I. Fakhr, *J. Heterocycl. Chem.*, 2016, **53**, 188.
8. H. Wen, L. Wang, L. B. Xu, Z. H. Hao, C.-L. Shao, C.-Y. Wang, and J. Xiao, *Adv. Synth. Catal.*, 2015, **357**, 4023; Y. Z. Zou, C. L. Chen, X. X. Chen, X. X. Zhang, and W. D. Rao, *Eur. J. Org. Chem.*, 2017, 2266.
9. L. Yu, D. Chen, J. Li, and P. G. Wang, *J. Org. Chem.*, 1997, **62**, 3575; M. Karthik, A. K. Tripathi, N. M. Gupta, M. Palanichamy, and V. Murugesan, *Catal. Commun.*, 2004, **5**, 371; G. Penieres-Carrillo, J. G. García-Estrada, J. L. Gutiérrez-Ramírez, and C. Alvarez-Toledano, *Green. Chem.*, 2003, **5**, 337;

S. Morteza, *Chem. Rev.*, 2012, **112**, 3508.

10. W.-R. Chao, D. Yean, K. Amin, C. Green, and L. Jong, *J. Med. Chem.*, 2007, **50**, 3412.
11. W. E. Noland, M. R. Venkiteswaran, and C. G. Richards, *J. Org. Chem.*, 1961, **26**, 4241; J. Bergman, P.-O. Norrby, U. Tilstam, and L. Venemalm, *Tetrahedron*, 1989, **45**, 5549; V. J. Rani, K. V. Vani, and C. V. Rao, *Synth. Commun.*, 2012, **42**, 2048.