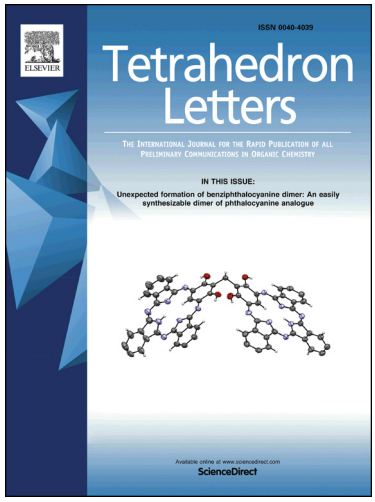

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Graphical Abstract

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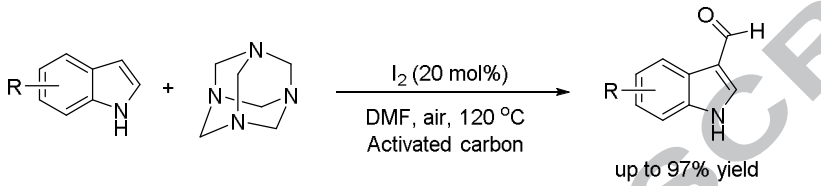

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Iodine-catalyzed C3-formylation of indoles using hexamethylenetetramine and air

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ABSTRACT

An efficient iodine-catalyzed chemoselective 3-formylation of free (N–H) and *N*-substituted indoles was achieved by using hexamethylenetetramine (HMTA) in the presence of activated carbon under air atmosphere. This new method could provide 3-formylindoles in moderate to excellent yields with fairly short reaction times. Moreover, this catalytic formylation of indoles procedure can be applied to gram-scale synthesis.

The indole nucleus is prevalent in natural and synthetic molecules with significant biological activities.[1] 3-Formylindoles are important precursors for the synthesis of a variety of indole derivatives because their carbonyl groups can readily undergo various transformations such as C-C and C-N coupling reactions, oxidations and reductions. Therefore, C-3 formylation is an important strategy to direct C-3 functionalization of indoles.[2] Traditionally, the Vilsmeier–Haack reaction is commonly applied for such transformation.[2] However, it requires a stoichiometric amount of toxic $POCl_3$, which is not environmentally benign. The Rieche[3], Duff[4] and Reimer-Tiemann[5] reactions are also powerful methods leading to 3-formylindoles, which generally require heating at elevated temperatures with excess amount of strong bases or acids in workup processes. Owing to the harsh reaction conditions, these traditional indole formylation methods are not compatible with the functional groups labile under strong acidic or basic conditions. Hence, the development of novel access to 3-formylindoles using environmentally benign reagents under mild conditions is still of much significance.

In 2011, Su and coworkers pioneered an elegant Ru-catalyzed C3-formylation of indoles using *N*-methylaniline as the carbonyl source.[6] The key strategy was the C–N bond cleavage of *N*-methylaniline through the formation of iminium ion intermediates. Subsequently, based on this strategy, several groups have reported *n*-Bu_4NI,[7a] KI,[7b] $CuCl_2$,[7c,d] I_2,[7e,f] Rose Bengal[7g] or Cerium(IV) ammonium nitrate (CAN)[7h] catalyzed C3-formylation of indoles using varied amines as the carbonyl source through C–N bond cleavage. However, excess pivalic acid (PivOH) was indispensable in Su[6] and Wang's[7a] strategies which was incompatible with the functional groups labile under acidic conditions. The utility of metal catalysts would result in several problems involved in removing the residual metals from the final products, which were usually a difficult and tedious process, limiting the practical applications of Su,[6] Li[7c], Cheng[7d] and Sakee's[7h] procedures. In 2013, Cheng and co-workers reported the NH_4OAc-promoted formylation of indole using DMSO as the carbonyl source, while this procedure has to process at an elevated temperature of 150 °C with prolonged reaction time.[8] Despite significant advances in the preparation of 3-formylindoles, the development of general, mild and operationally simple methods for the formylation of indoles is highly desirable. Herein, we report a simple and practical molecular iodine-catalyzed C3-selective formylation of free (N-H) and *N*-substituted indoles by using hexamethylenetetramine (HMTA) as the carbon source and air as the oxidant.

We began our investigation by using indole **1a** (1.0 mmol) and HMTA (2.0 mmol) as the model substrates in the presence of *tert*-butyl hydroperoxide (TBHP) (2.0 mmol) and *n*-Bu_4NI (10 mol%). The results were summarized in Table 1. After screening various common solvents at 25 °C, all of them did not react at all (Table 1, entries 1-4). When using molecular iodine (1.0 equiv) instead of *n*-Bu_4NI as the promotor, indole **1a** was consumed within 5 h at 50 °C in MeOH as determined by TLC, while 3-iodo-1*H*-indole was the primary product which was detected by GC-MS and confirmed by the comparison with product from literature procedure (Table 1, entry 5).[9] When the procedure was performed under reflux condition, a trace amount of the desired formylation product was detected by GC-MS (Table 1, entry 6).

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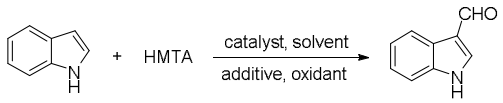
Table 1. Optimization of reaction conditions.[a]



1a **2a**

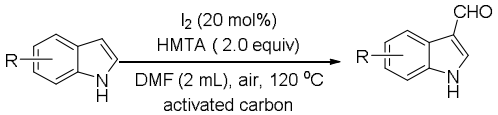
Entry	Catalyst (equiv)	Oxidant (equiv)	Additive	Solvent	T(°C)	t (h)	Yield[b] (%)
1	nBu$_4$NI (10 mol%)	TBHP (2.0 eq.)	-	DMF	25	12	N.R.[c]
2	nBu$_4$NI(10 mol%)	TBHP (2.0 eq.)	-	DMSO	25	12	N.R.[c]
3	nBu$_4$NI(10 mol%)	TBHP (2.0 eq.)	-	MeCN	25	12	N.R.[c]
4	nBu$_4$NI(10 mol%)	TBHP (2.0 eq.)	-	1,4-Dioxane	25	12	N.R.[c]
5	I_2(1.0 eq.)	TBHP (2.0 eq.)	-	MeOH	50	5	0 [d]
6	I_2(1.0 eq.)	TBHP (2.0 eq.)	-	MeOH	reflux	12	trace
7	I_2(1.0 eq.)	air	-	MeOH	reflux	20	21
8	I_2(1.0 eq.)	air	-	1,4-Dioxane	reflux	12	33
9	I_2(1.0 eq.)	air	-	DMF	100	10	51
10	I_2(1.0 eq.)	air	activated carbon (0.1 g)	DMF	100	6	97
11	I_2(1.0 eq.)	air	activated carbon (0.1 g)	DMF	120	0.8	97
12	I_2(1.0 eq.)	air	activated carbon (0.1 g)	DMF	130	0.8	94
13	I_2(20 mol%)	air	activated carbon (0.1 g)	DMF	120	0.8	97
14	I_2(10 mol%)	air	activated carbon (0.1 g)	DMF	120	24	30
15[e]	I_2(20 mol%)	air	activated carbon (0.1 g)	DMF	120	8	45
16	I_2(20 mol%)	air	activated carbon (0.05 g)	DMF	120	10	83

[a] Reaction conditions: indole **1a**(1.0 mmol, 0.1172 g), HMTA (2.0 mmol, 0.2804 g), solvent (2 mL).
[b] Isolated yields based indole.
[c] N.R. = no reaction.
[d] detected by GC-MS.
[e] HMTA (1.1 equiv).

Interestingly, when the mixture of indole **1a**, HMTA and molecular iodine was stirred in the open air without TBHP under reflux condition in MeOH for 20 h, the desired formylation product 1*H*-indole-3-carbaldehyde **2a** was isolated in 21% yield (Table 1, entry 7). After the solvent was switched to 1,4-dioxane, the yield increased slightly to 33%(Table 1, entry 8). Excitedly, when DMF was used, the yield increased significantly to 51% (Table 1, entry 9). Encouraged by this result and inspired by Hayashi's reports,[10] activated carbon (0.1 g) was used as the additive. Surprisingly, the yield increased dramatically to 97% (Table 1, entry 10). Furthermore, when performing the formylation at an elevated temperature of 120 °C, the reaction time reduced from 6 h to 50 min and the yield was still excellent (Table 1, entry 11). However, a higher temperature of 130 °C led to a decreased yield of 94% (Table 1, entry 12). When a reduced amount of molecular iodine (20 mol%) was employed, the yield and reaction time remained unchanged (Table 1, entry 13). Further decreasing the amount of molecular iodine to 10 mol % resulted in lower yield and prolonged reaction time (Table 1, entry 14). Similar results were obtained when the amount of HMTA or activated carbon was reduced (Table 1, entry 15 and 16).

With the optimized reaction conditions in hand (Table 1, entry 13), we further pursued the scope of the formylation reaction. A series of indoles **1** with different substituents on benzene and pyrrole rings, including nitrogen atoms, were examined, and the results were summarized in Table 2. Moreover, the yields of the desired products were compared with those reported in related literatures.[6,7,8,11,12] When 2-methylindole **1b** was submitted to the standard conditions, only a trace amount of the desired formylation product was detected by GC-MS, probably owing to its electron-richness which makes it unstable under oxidative conditions,[6] yet 2-phenylindole **1c** successfully gave desired formylation product in 70% yield (Table 2, entries 2 and 3). Notably, in the case of 3-methylindole **1d**, no reaction took place as determined by GC-MS (Table 2, entry 4). Evidently, the formylation predominantly took place on the C-3 of indoles, as no regioisomeric product was observed by GC-MS. As expected, indoles with a range of substituents in all positions on the benzene rings were compatible with this novel formylation procedure, and generated the corresponding products in moderate to excellent yields (Table 2, entries 5-12). Compared with electron-donating groups, electron-withdrawing groups lowered the yields and prolonged the reaction times (Table 2, entries 5-9 *vs* entries 10-12). Moreover, the scope was also extended to some *N*-substituted indoles which afforded the desired products in reasonable to good yields (Table 2, entries 13-19). Unexpectedly, after being processed under our standard condition for 30 h,

Table 2. Scope of the substrates.[a]



1a-q **2a-q**

Entry	Indole	R	Product	t (h)	Yield[b, c](%)
1	**1a**	H	**2a**	0.8	97 (81[6], 82[7a], 52[7g], 66[7f])
2	**1b**	2-Me	**2b**	1	Trace (63[7e], 44[7f])
3	**1c**	2-Ph	**2c**	4	70 (61[7d], 88[7h])
4	**1d**	3-Me	**2d**	12	N.R.[d] (30[8])[e]
5	**1e**	4-Me	**2e**	1.5	81 (83[11])

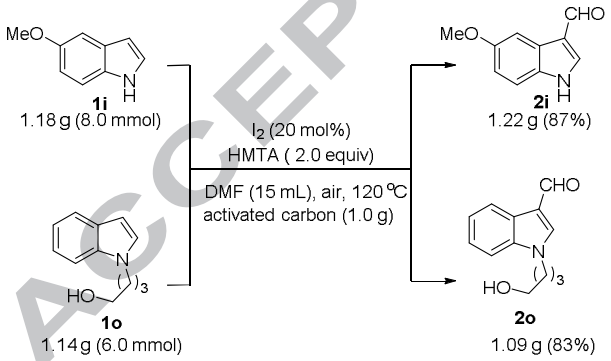
Table 2. (continued)

Entry	Indole	R	Product	t (h)	Yield[b, c](%)
6	**1f**	5-Me	**2f**	0.8	92 (71[6],70[7e], 59[7f])
7	**1g**	6-Me	**2g**	0.8	91 (92[11])
8	**1h**	7-Me	**2h**	1.5	89 (82[8], 96[11])
9	**1i**	5-OMe	**2i**	0.8	91 (70[6], 72[7e], 57[7f], 60[7h])
10	**1j**	5-Br	**2j**	4	65 (73[6], 57[7a], 70[7e], 82[7f])
11	**1k**	7-Br	**2k**	8.5	66 (60[7f])
12	**1l**	5-NO_2	**2l**	19	57 (47[7f], 86[11])
13	**1m**	*N*-Me	**2m**	4	86 (83[7d], 78[7a], 79[8], 83[7e])
14	**1n**	*N*-Et	**2n**	5.5	82 (83[7d], 74[7e], 44[7f], 60[7g])
15	**1o**	*N*-$(CH_2)_4OH$	**2o**	4	87(85[12])
16	**1p**	*N*-Bn	**2p**	10	53 (75[7a], 79[7d], 70[7e], 42[7f])
17	**1q**	*N*-allyl	**2q**	9	34 (77[7d], 50[7e], 55[7g])
18	**1r**	*N*-$CH_2CH(OEt)_2$	**2r**	4.5	84
19	**1s**	*N*-$(CH_2)_4OAc$	**2s**	5	86
20	**1t**	*N*-Ac	**2t**	30	Trace[f]

[a] Reaction conditions: indole **1a-q** (1.0 mmol), HMTA (2.0 mmol, 0.2804 g), I2 (0.2 mmol, 0.0507g), DMF (2 mL), activated carbon (0.1 g), 120 °C, under air.
[b] Isolated yields based indole.
[c] Values in parentheses are the yields reported in the related literatures.
[d] N.R. = no reaction.
[e] C2-Formylation product was formed.
[f] 94% of the starting material **1t** was recovered.

N-acetylindole **1t** gave only a trace amount of the desired formylation product as detected by TLC and GC-MS, and 94% of **1t** was recovered, which may due to the electron-withdrawing effect of the acetyl group (Table 2, entry 20). Notably, C-Br bond, free hydroxyl, acetal and ester were still intacted during the reactions (Table 2, entries 10, 11, 15, 18 and 19), providing an additional handle for further elaboration of products.

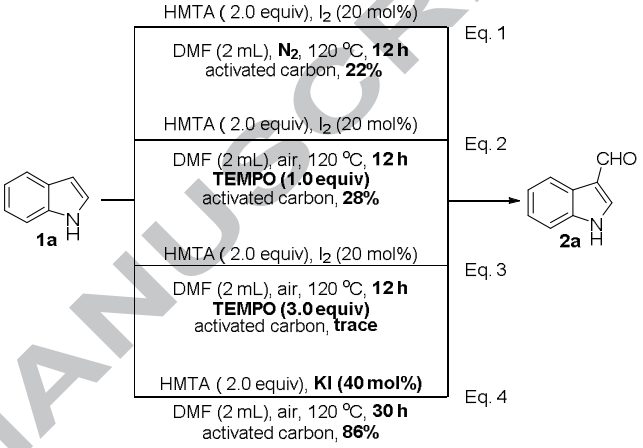
Furthermore, the formylation procedure could be applied to gram-scale synthesis. For example, when 5-methoxy-1*H*-indole **1i** or 1-(4-hydroxybutyl)-1*H*-indole **1o** was processed on about 1 gram scale, both of them gave good yields after recrystallization of the crude products from C_2H_5OH-H_2O (V/V = 1 : 3) (Scheme 1).



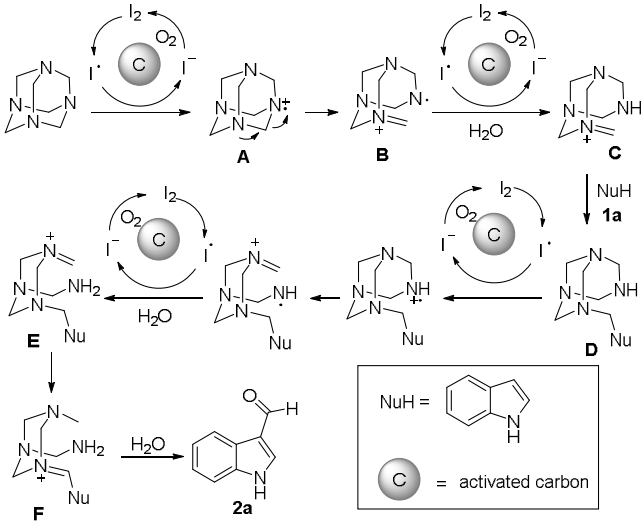
Scheme 1. Gram-scale C3-formylation of typical indoles.

With the success of the protocol applying indoles, several electron-rich aromatic systems such as *N*,*N*-dimethylaniline, 1,3,5-trimethoxybenzene, 2,4-di-*tert*-butylphenol and 2,6-dimethoxyphenol were investigated, and no formylation reaction was observed.

To gain insight into the reaction pathway, further experiments were conducted and outlined in Scheme 2. When the reaction was processed under N_2, the yield of the desired product **2a** sharply declined from 97% to 22%, indicating that molecular oxygen from air was essential in our system (Scheme 2, Eq. 1). When 1.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a radical inhibitor, was added into the reaction system under the standard reaction conditions, the yield of the desired product **2a** decreased dramatically to 28% (Scheme 2, Eq. 2). Moreover, when 3.0 equiv of TEMPO was used, the reaction only gaved a trace amount of the desired product **2a** (Scheme 2, Eq. 3). These results revealed that radical intermediates were involved in the catalytic cycle. When using KI (40 mol%) as the catalyst, the desired product was obtained in 86% yield after 30 h, suggesting that iodide anion was usable but not efficient enough (Scheme 2, Eq. 4). It is reasonable to suppose that a step giving iodide anion and a step oxidizing iodide anion to molecular iodine are elements of the catalytic cycle.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction mechanism.

According to the results mentioned above and the related literature[7], a possible mechanism was proposed as shown in Scheme 3. Radical cation **A** is generated through the transfer of the iodine radical species from homolytic cleavage of molecular iodine. The radical cation then undergoes fragmentation to give intermediate **B**, an iminium cation with an amine radical. Intermediate **B** further is oxidized to yield iminium ion **C**. Subsequently, nucleophilic attack of indole **1a** to **C** affords intermediate **D**. Intermediate **D** undergoes a similar process to

give the second iminium ion **E**, followed by a 1,5-hydrogen shift to give iminium ion **F** which is hydrolyzed by H_2O to give the desired product 1*H*-indole-3-carbaldehyde **2a**.

In conclusions, we described a simple and practical method for the C3-formylation of free (N–H) and *N*-substituted indoles using HMTA as the carbon source. This procedure was conducted under air using molecular iodine as the catalyst, avoiding the use of harmful transition-metal catalyst and peroxide oxidant. 3-Formylindoles with both electron-donating and electron-withdrawing groups were obtained in moderate to excellent yields with fairly short reaction times. The protocol might be useful for the synthesis of indoles bearing acid- or base-sensitive functional groups. Moreover, this procedure can also be applied to gram-scale synthesis and represents an exceedingly attractive alternative to the traditional formylation methods.

Acknowledgments

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Supplementary data

Supplementary data associated with this letter can be found in the online version, at http://dx.doi.org/10.1016/ /j.tetlet.000000

References and notes

1. (a) Sravanthi TV, Manju SL. *Eur J Pharm Sci*. 2016;91:1–10;
(b) Sugimoto S, Naganuma M, Kanai T. *J Gastroenterol*. 2016;51:853–861;
(c) Almagro L, Fernández-Pérez F, Pedreño M. *Molecules*. 2015;20:2973–3000;
(d) Zhang M-Z, Chen Q, Yang G-F. *Eur J Med Chem*. 2015;89:421–441;
(e) Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. *Nat Prod Rep*. 2014;31:160;
(f) França PHB, Barbosa DP, da Silva DL, Ribeiro ÊAN, Santana AEG, Santos BVO, Barbosa-Filho JM, Quintans JSS, Barreto RSS, Quintans-Júnior LJ, Araújo-Júnior JX. *Biomed Res Int*. 2014;2014:1–12;
(g) Sakai R, Swanson GT. *Nat Prod Rep*. 2014;31:273–309;
(h) Kaushik N, Kaushik N, Attri P, Kumar N, Kim C, Verma A, Choi E. *Molecules*. 2013;18:6620–6662;
(i) Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. *Nat Prod Rep*. 2012;29:144–222.
(j) Kochanowska-Karamyan AJ, Hamann MT. *Chem Rev*. 2010;110:4489–4497.
(k) Somei M, Yamada F. *Nat Prod Rep*. 2005;22:73;
2. (a) Yang M-R, Qin Y-J, Chen C, Zhang Y-L, Li B-Y, Liu T-B, Gong H-B, Wang B-Z, Zhu H-L. *RSC Adv*. 2016;6:30412–30424;
(b) Netz N, Opatz T. *J Org Chem*. 2016;81:1723–1730;
(c) Das Mukherjee D, Kumar NM, Tantak MP, Das A, Ganguli A, Datta S, Kumar D, Chakrabarti G. *Biochemistry*. 2016;55:3020–3035;
(d) Sundaree S, Vaddula BR, Tantak MP, Khandagale SB, Shi C, Shah K, Kumar D. *Med Chem Res*. 2016;25:941–950;
(e) Pedada SR, Yarla NS, Tambade PJ, Dhananjaya BL, Bishayee A, Arunasree KM, Philip GH, Dharmapuri G, Aliev G, Putta S, Rangaiah G. *Eur J Med Chem*. 2016;112:289–297;
(f) Zhang Y-L, Qin Y-J, Tang D-J, Yang M-R, Li B-Y, Wang Y-T, Cai H-Y, Wang B-Z, Zhu H-L. *ChemMedChem*. 2016;11:1446–1458;
(g) El-labbad EM, Ismail MAH, Abou Ei Ella DA, Ahmed M, Wang F, Barakat KH, Abouzid KAM. *Chem Biol Drug Des*. 2015;86:1518–1527.
(h) Chen C-H, Genapathy S, Fischer PM, Chan WC. *Org Biomol Chem*. 2014;12:9764–9768;
(i) Sashidhara K V, Dodda RP, Sonkar R, Palnati GR, Bhatia G. *Eur J Med Chem*. 2014;81:499–509;
(j) Jin H, Zhang P, Bijian K, Ren S, Wan S, Alaoui-Jamali MA, Jiang T. *Mar Drugs*. 2013;11:1427–1439.
3. (a) Bennasar M-L, Zulaica E, Solé D, Alonso S. *Tetrahedron*. 2007;63:861–866;
(b) Tohyama S, Choshi T, Matsumoto K, Yamabuki A, Ikegata K, Nobuhiro J, Hibino S. *Tetrahedron Lett*. 2005;46:5263–5264;
(c) Mayer S, Joseph B, Guillaumet G, Mérour J-Y. *Synthesis*. 2002;2002:1871–1878.
4. (a) Van Niel MB, Collins I, Beer MS, Broughton HB, Cheng SKF, Goodacre SC, Heald A, Locker KL, MacLeod AM, Morrison D, Moyes CR, O'Connor D, Pike A, Rowley M, Russel N, Sohal BB, Stanton JA, Thomas S, Verrier H, Watt AP, Castro JLJL, Russell MGN, Sohal BB, Stanton JA, Thomas S, Verrier H, Watt AP, Castro JLJL. *J Med Chem*. 1999;42:2087–2104;
(b) Chatterjee A, Biswas KM. *J Org Chem*. 1973;38:4002–4004.
5. (a) Wynberg H. *Chem Rev*. 1960;60:169–184;
(b) Blume RC, Lindwall HG. *J Org Chem*. 1945;10:255–258;
6. Wu W, Su W. *J Am Chem Soc*. 2011;133:11924–11927;
7. (a) Li L-T, Huang J, Li H-Y, Wen L-J, Wang P, Wang B. *Chem Commun*. 2012;48:5187–5189;
(b) Li L-T, Li H-Y, Xing L-J, Wen L-J, Wang P, Wang B. *Org Biomol Chem*. 2012;10:9519–9522;
(c) Zhang L, Peng C, Zhao D, Wang Y, Fu H-J, Shen Q, Li J-X. *Chem Commun*. 2012;48:5928;
(d) Chen J, Liu B, Liu D, Liu S, Cheng J. *Adv Synth Catal*. 2012;354:2438–2442;
(e) Zhang B, Liu B, Chen J, Wang J, Liu M. *Tetrahedron Lett*. 2014;55:5618–5621;
(f) Lu L, Xiong Q, Guo S, He T, Xu F, Gong J, Zhu Z, Cai H. *Tetrahedron*. 2015;71:3637–3641;
(g) Li X, Gu X, Li Y, Li P. *ACS Catal*. 2014;4:1897–1900;
(h) Tongkhan S, Radchatawedchakoon W, Kruanetr S, Sakee U. *Tetrahedron Lett*. 2014;55:3909–3912.
8. Fei H, Yu J, Jiang Y, Guo H, Cheng J. *Org Biomol Chem*. 2013;11:7092–7095;
9. Witulski B, Buschmann N, Bergstrasser U. *Tetrahedron*. 2000;56:8473–8480;
10. (a) Kawashita Y, Nakamichi N, Kawabata H, Hayashi M. *Org Lett*. 2003;5:3713–3715;
(b) Kawabata H, Hayashi M. *Tetrahedron Lett*. 2004;45:5457–5459;
(c) Sano Y, Tanaka T, Hayashi M. *Chem Lett*. 2007;36:1414–1415;
(d) Hayashi M. *Chem Rec*. 2008;8:252–267;
(e) Kawashita Y, Yanagi J, Fujii T, Hayashi M. *Bull Chem Soc Jpn*. 2009;82:482–488;
(f) Kawashita Y, Hayashi M. *Molecules*. 2009;14:3073–3093.
11. Xu H, Yang W, Wang Q, bin Yang W, Wang Q, Yang W, Wang Q. *Chem Biol Drug Des*. 2011;78:864–868.
12. Naik PN, Naik NH, Khan A, Kusurkar RS. *Tetrahedron*. 2013;69:6545–6551.

Highlights

The formylation procedure is transition-metal-free, using molecular iodine as catalyst.
Air in the presence of activated carbon is the oxidant of the formylation procedure.
The reaction time of the formylation procedure is fairly short.
This formylation procedure can be applied to gram-scale synthesis.