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PII: S0040-4039(17)31489-2
DOI: https://doi.org/10.1016/j.tetlet.2017.11.055
Reference: TETL 49498

To appear in: *Tetrahedron Letters*

Received Date: 8 October 2017
Revised Date: 27 November 2017
Accepted Date: 28 November 2017

Please cite this article as: Yahyavi, H., Heravi, M.M., Mahdavi, M., Foroumadi, A., Iodine-catalyzed tandem oxidative coupling reaction: a one-pot strategy for the synthesis of new coumarin-fused pyrroles, *Tetrahedron Letters* (2017), doi: https://doi.org/10.1016/j.tetlet.2017.11.055

Iodine-catalyzed tandem oxidative coupling reaction: a one-pot strategy for the synthesis of new coumarin-fused pyrroles

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Abstract. The simple and facile strategy for the synthesis of 2,3-disubstituted-chromeno[4,3-*b*]pyrrole-4(1*H*)-ones has been established. This method describes the Kornblum oxidation reaction of acetophenones, followed by the Knoevenagle treatment of the resulted (het)arylglyoxals with active methylene compounds and consequently iodine-activated Michael type reaction with 4-amino coumarin in a one-pot manner to afford disubstituted chromeno[4,3-*b*]pyrrole-4(1*H*)-one derivatives.

Key words: 2,3-*Di*substituted chromeno[4,3-*b*]pyrrole-4(1*H*)-ones; Kornblum oxidation reaction; Iodine; Michael type reaction.

Introduction

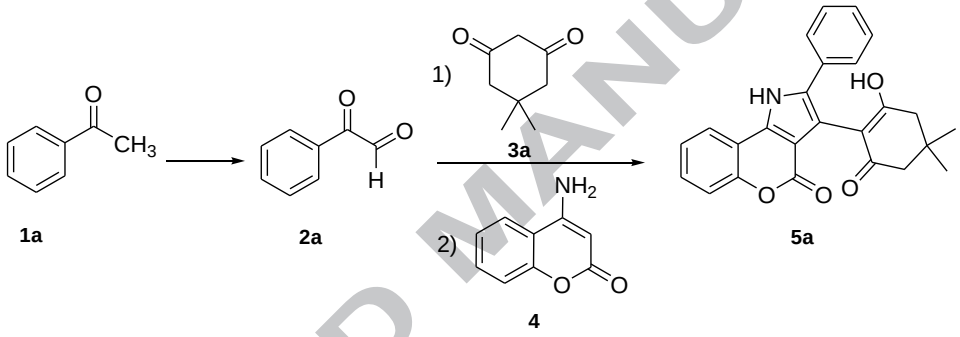
Chromene and pyrrole are important heterocyclic motifs in biomolecules and setting these rings in one compound creates important systems, which are found as the basic building block in several bioactive compounds including marine alkaloids ningalin B and lamellarin D.[1-3] Many synthetic protocols have been reported for the synthesis of chromeno[4,3-*b*]pyrrole-4(1*H*)-ones, an important fused heterocyclic core consisting chromene and pyrrole, including the reaction of *β*-nitroalkenes and 4-phenylamino coumarins under solvent–free condition[4] and the reaction of amine, glyoxal monohydrate and 4-amino coumarin in the presence of nanocrystalline $CuFe_2O_4$[5] and $KHSO_4$.[6] 4-Chloro coumarin was reported as starting material in literature and reacted with α-amino ketones[7] and α-amino acid derivatives to produce *N*-(α)-(2-oxo-2*H*-1-benzopyran-4-yl)Weinreb-α-aminoamides.[8] In addition, the reaction of 4-*N*-(4′-aryloxybut-2-ynyl)-*N*-methylaminocoumarins with 3-chloroperoxybenzoic acid afforded the desired pyrrolo[3,2-*c*]coumarin derivatives.[9]

The assembly of N-heterocycles by designing new catalytic systems has attracted the chemists' attention. Since the first application of molecular iodine as a catalytic system in the conversion of diacetone alcohol into mesityl oxide in 1915,[10] the catalytic applications of iodine in organic synthesis and in chemical technology have become the focus of organic chemists in functional group transformation.[11] Two modes of activation have been proposed for iodine-catalyzed reactions, meaning iodine-bond activation and hidden Brønsted acid catalysis.[12] Among these approaches,[13-16] the first one has been favored in catalytic reactions over another pathway, especially in Michael type reactions. By combining the advantageous features of tandem reactions and iodine as a catalyst, a powerful synthetic strategy has been presented in this report for the construction of complex structure, chromeno[4,3-*b*]pyrrole-4(1*H*)-ones, from simple substrates. In continuation of our efforts to introduce economic and environmentally benign methods for the synthesis of heterocyclic compounds,[17] herein, we report a novel I_2-catalyzed, four-component approach towards chromeno[4,3-*b*]pyrrole-4(1*H*)-ones. The reaction entails the *in situ* synthesis of 2-oxo-2-arylacetaldehyde *via* the Kornblum oxidation reaction from the corresponding acetophenone derivatives in the presence of molecular iodine and DMSO.[18]

We started our quest for the *in situ* synthesis of 2-oxo-2-phenylacetaldehyde (phenylglyoxal), by the Kornblum oxidation reaction of acetophenone, according to previously reported procedure.[18] After purification, we performed the one-pot reaction between phenyl glyoxal, 4-amino coumarin and dimedone in DMSO at 100 ^{o}C. To find a suitable catalyst, the reaction was screened by utilizing

different acidic catalysts such as TsOH-H_2O, HOAc, $ZnCl_2$, $FeCl_3$ and I_2 (Table 1, entries 1-5). It was found that iodine afforded the desired product **5a** in better yields. Since iodine was also effective in the preparation of compound **2a**, we decided to attempt the reaction in a one-pot manner. Relied on similar isolated yields (Table 1, entry 6) and advantageous features of one-pot reaction, allowing easy purification and preparation, we chose this condition for further optimization and derivatization. Subsequently, with the intention of finding optimized temperature and iodine amount, the model reaction was evaluated at different temperatures (80, 90 and 110 ^oC) (Table 1, entries 7-9) and iodine amount (1.2 equiv.) (Table 1, entry 10). The best condition for this reaction was determined heating the starting materials at 100 ^oC by utilizing 1.1 equiv. iodine.

Table 1. Optimization of reaction condition [a]



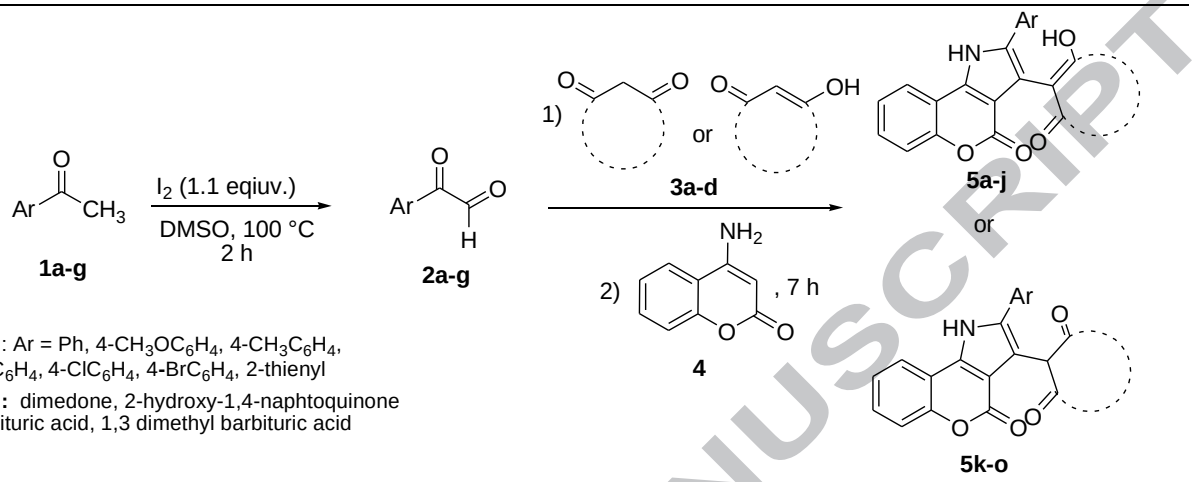
Entry	T (^oC)	Catalyst	Yield (%)
1[a]	100	TsOH-H_2O	60[b]
2[a]	100	HOAc	55
3[a]	100	$ZnCl_2$	35
4[a]	100	$FeCl_3$	32
5[a]	100	I_2	79
6[c]	**100**	I_2	**86**
7	80	I_2	41
8	90	I_2	65
9	110	I_2	85
10[d]	100	I_2	85

[a] Reaction conditions: phenyl glyoxal (1 mmol), dimedone (1 mmol), 4-amino coumarin (1 mmol) and acidic catalyst (1.1 equiv.) were heated in DMSO at 100 ^oC for 7 h. [b] Isolated yields. [c] Acetophenone (1 mmol) and iodine (1.1 equiv.) were heated in DMSO at 100 ^oC for 2 h, then dimedone (1 mmol) and 4-amino coumarin (1 mmol) were added and the reaction was continued for 7 h. [d] 1.2 equiv. of iodine was used.

Encouraged by this success, we extended this reaction to a series of (het)aryl methyl ketones **1a-g** and 1,3-dicarbonyl compounds **3a-d** under optimized condition and corresponding

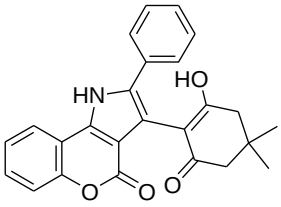
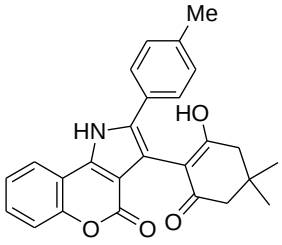
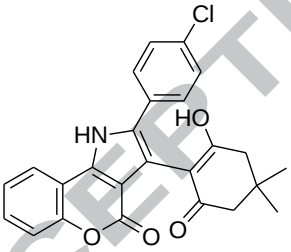
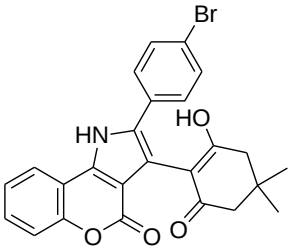
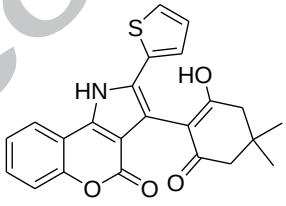
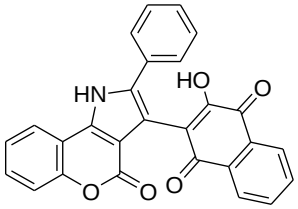
chromeno[4,3-*b*]pyrroles **5a-o** were obtained in high yields.[20] The results are summarized in Table 2.

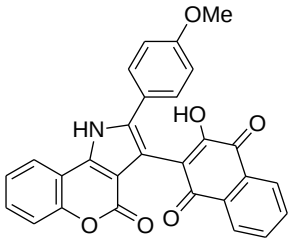
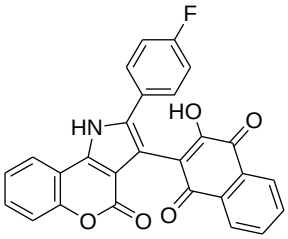
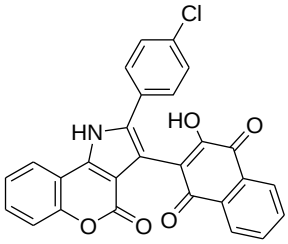
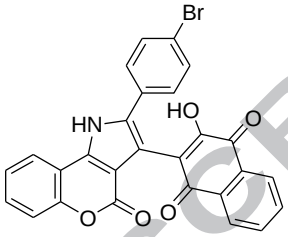
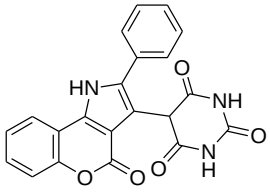
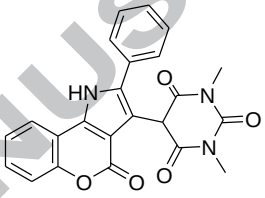
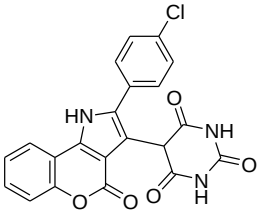
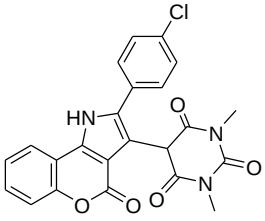
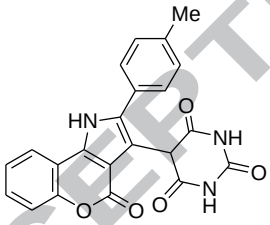
Table 2. Substrate scope for the one-pot synthesis of chromeno[4,3-*b*]pyrrol-4(1*H*)-ones **5a-o**



1a-g: Ar = Ph, 4-$CH_3OC_6H_4$, 4-$CH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-thienyl

3a-d: dimedone, 2-hydroxy-1,4-naphtoquinone barbituric acid, 1,3 dimethyl barbituric acid

Product	Structure	Yield (%)[a]	Product	Structure	Yield (%)[a]
5a		**86**	**5b**		**78**
5c		**89**	**5d**		**82**
5e		**80**	**5f**		**76**

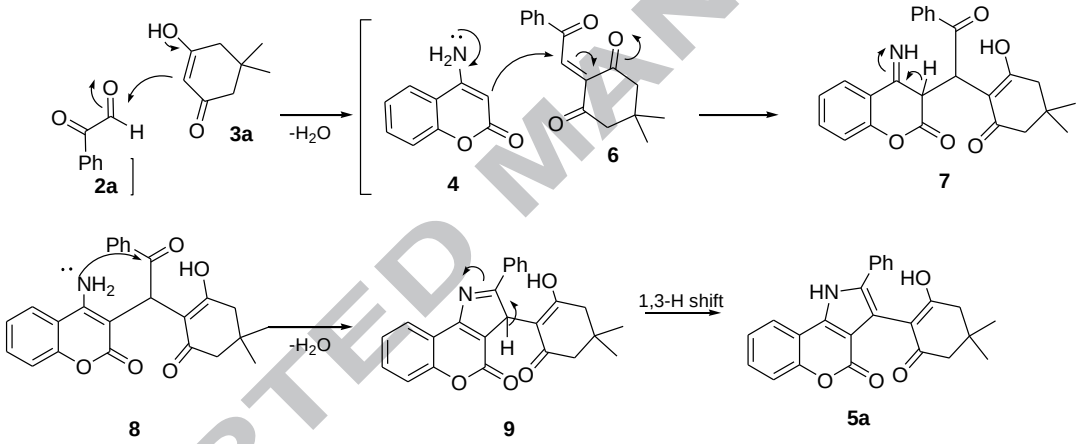
5g		**81**	**5h**		**73**
5i		**79**	**5j**		**76**
5k		**73**	**5l**		**85**
5m		**86**	**5n**		**88**
5o		**77**			

[a] Isolated yields.

The structures of the isolated products were deduced by IR, ^{1}H, ^{13}C NMR spectroscopy, mass spectrometry and elemental analyses.[19] For example, the IR spectrum of **5a** showed the stretching bands for N−H, and C=O bonds at 3339 (sharp), 1721 and 1613 cm^{-1}, respectively. The ^{1}H NMR spectrum of **5a** exhibited two singlets at 1.06 and 1.17 ppm related to methyl groups. The methylene groups of dimedone appeared at 2.42 and 2.50 ppm as two singlets as well as the characteristic signals with appropriate chemical shifts and coupling constants at 7.30-

8.24 ppm related to the nine aromatic H-atoms. In addition, the sharp singlet at 10.14 and 12.49 ppm are related to the NH of pyrrole ring and enolic OH, respectively. The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed characteristic signals at 27.9, 28.2, 31.6, 42.9 and 50.5 ppm for the dimedone moiety. Also, 18 distinguishing signals were observed in 107-195 ppm, arising from the aromatic and carbonyl groups of the desired product.

The proposed mechanism for this reaction is provided in Scheme 2. Mechanistically, it is conceivable that the reaction involves the initial formation of phenylglyoxal **2a**,[20] followed by the Knoevenagle condensation reaction with dimedone **3a** and formation of adduct **6**, which was assisted by molecular iodine *via* the activation of aldehyde group. Then, Michael type addition of 4-aminocoumarin to intermediate **6,** imine-enamine rearrangement, annulation and elimination of H_2O furnished intermediate **9**. The latter undergoes proton shift to afford 3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-phenylchromeno[4,3-*b*]pyrrole-4(1*H*)-one **5a**.



Scheme 2. The proposed mechanism for the synthesis of 3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-phenylchromeno[4,3-*b*]pyrrole-4(1*H*)-one.

In conclusion, we have developed an efficient, I_2-catalyzed approach for the synthesis of 3-substituted-2-(het)arylchromeno[4,3-*b*]pyrrole-4(1*H*)-ones. Considering the availability of the starting materials, nontoxic and nonmetallic characteristics of iodine, easy work-up and high yields of the desired products, this approach provides a straightforward route to construct novel chromeno[4,3-*b*]pyrrole derivatives. The synthesized compounds in the present study may find useful applications in synthetic organic and medicinal chemistry.

Acknowledgments

This study was funded and supported by Iran National Science Foundation (INSF).

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19. **General Procedure for the Preparation of 5a**: A mixture of acetophenone (0.120 g, 1 mmol) and molecular iodine (0.140 g, 1.1 mmol) in DMSO (10 mL) was stirred at 100 °C for 2 h. Upon completion, as indicated by TLC analysis, dimedone (0.140 g, 1 mmol) and 4-amino coumarin (0.168 g, 1 mmol) were added to the mixture, respectively and the mixture was allowed to stir for another 7 h at 100 °C. After this time, the reaction mixture was cooled and poured into the ice/water mixture (50 mL). The resulting precipitate was filtered, washed with hot EtOH and dried to afford the pure product **5a**.

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-phenylchromeno[4,3-*b*]pyrrole-4(1*H*)-one (**5a**):

Yield: (0.34 g, 86%); White powder, mp >300 °C, IR (KBr) (ν_{max}/cm^{-1}): 3339 (NH), 3053, 2963, 2865, 1721 (broad, C=O), 1613, 1508, 1465, 1368, 1203, 1116, 1030, 954, 754, 684. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.06 and 1.17 (2s, 6H, 2CH$_3$), 2.42 and 2.50 (2s, 4H, 2CH$_2$), 7.31 (t, *J* = 7.0 Hz, 1H), 7.36-7.46 (m, 5H), 7.55 (d, *J* = 7.5 Hz, 2H), 8.24 (d, *J* = 7.5 Hz, 1H), 10.14 (s, 1H, NH), 12.50 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 27.9 and 28.2 (2CH$_3$), 31.6 (C(CH$_3$)$_2$), 42.9 and 50.4 (2CH$_2$), 107.2, 109.2 (−C=C−OH), 113.8, 116.4, 116.7, 121.3, 123.7, 126.6, 126.8, 128.2, 128.4, 131.9, 134.3, 134.9, 151.1 (O−C=O), 157.1 (C−O), 171.4 (C−OH), 195.9 (C=O). EI-MS *m/z* (%): 399 (M$^+$, 100), 384 (78), 301 (47), 286 (11), 274 (31), 245 (9), 172 (90), 216 (14), 126 (6), 55 (11). Anal. Calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.39; H, 5.42; N, 3.68.

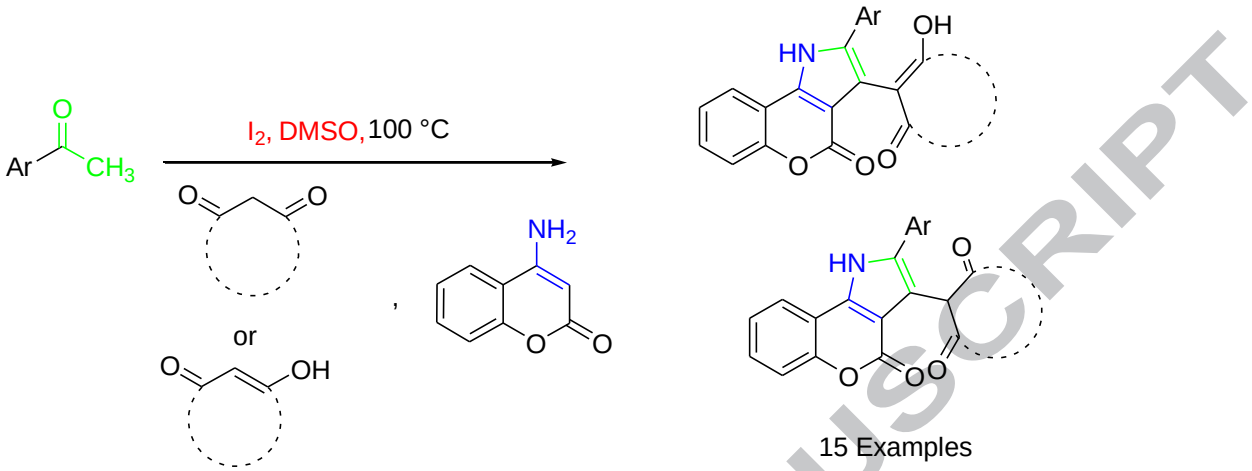
2-Hydroxy-3-(4-oxo-2-phenyl-1,4-dihydrochromeno[4,3-*b*]pyrrol-3-yl)naphthalene-1,4-dione (5f):

Yield 0.33 g, (76%); Red powder, mp >300 ˚C, IR (KBr) (ν_{max}/cm^{-1}): 3345 (NH), 3253, 3224, 1678 (broad, C=O), 1590, 1506, 1461, 1358, 1203, 1158, 1130, 1040, 752, 721. ^{1}H NMR (500 MHz, DMSO-d_6): 7.31 (s, 1H, CH), 7.39-7.47 (m, 4H, 4CH), 7.49 (t, *J* = 7.5 Hz, 1H, CH), 7.61 (d, *J* = 7.5 Hz, 2H, 2CH), 7.84-7.90 (m, 2H, 2CH), 7.99 (d, *J* = 7.5 Hz, 1H, CH), 8.10 (d, *J* = 7 Hz, 1H, CH), 8.30 (d, *J* = 7.5 Hz, 1H, CH), 11.14 (s, 1H, pyrrole NH), 12.82 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6): 109.4 (−C=C−OH), 110.2 (C pyrrole), 114.0 (C), 117.3 (CH), 118.0 (C pyrrole), 122.2 (CH), 124.7 (CH), 126.6 (CH), 127.1 (2CH), 128.3 (CH), 129.2 (2CH), 130.7 (C), 131.8 and 132.6 (2C of pyrrole), 133.8 (CH), 135.3 (CH), 136.0 (C), 151.8 (C), 157.7 (O−C=O), 181.4 (C=O), 183.7 (C=O). EI-MS, *m/z* (%): 433 (M$^+$, 100), 405 (79), 388 (5), 376

(9), 360 (8), 348 (23), 320 (7), 301 (6), 272 (5), 216 (6), 104 (19), 76 (17). Anal. Calcd. for $C_{27}H_{15}NO_5$: C, 74.82; H, 3.49; N, 3.23. Found: C, 74.65; H, 3.67; N, 3.01.

20. (a) Yin G, Wang Z, Chen A, Gao M, Wu A, Pan Y. *J Org Chem*. 2008;73:3377-3383.
(b) Yin G, Zhou B, Meng X, Wu A, Pan Y. *Org Lett*. 2006;8:2245-2248.

Graphical Abstract:



Highlights

The new method for the synthesis of chromeno[4,3-*b*]pyrrol-4(1*H*)-ones is reported.

In this method, iodine is utilized as nontoxic and nonmetallic catalyst.

Iodine conducted Kornblum oxidation and Michael type reaction in one-pot manner.