

Article

Synthesis of Highly Substituted Oxazoles through Iodine(III)-Mediated Reactions of Ketones with Nitriles

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Abstract: In the presence of trifluoromethanesulfonic acid (TfOH) or bis(trifluoromethanesulfonyl)imide (Tf₂NH), iodosobenzene (PhI=O) efficiently promoted the reactions of dicarbonyl compounds as well as monocarbonyl compounds with nitriles to give 2,4-disubstituted and 2,4,5-trisubstituted oxazole in a single step under the mild conditions.

Keywords: single-step synthesis; iodine(III); oxazole; ketone; nitrile

1. Introduction

The synthesis of oxazole compounds has attracted a great deal of attention due to the widespread application of oxazole derivatives in biologically active compounds as well as versatile building blocks in organic synthesis [1–3]. For the purpose of synthesizing highly substituted oxazole compounds, an intramolecular reaction, the so-called Robinson-Gabriel cyclocondensation of α -acylamino ketones in the presence of dehydrating reagents [H₂SO₄, POCl₃, (CF₃SO₂)₂O, and so on] has been commonly employed [4–6]. As for the intermolecular approaches to highly substituted oxazoles, α -diazo ketones [7–9], α -halo ketones [10,11], α -sulfonyloxy ketones [12], and iodonium ylides of ketones [13] have been used as a reactive synthetic intermediate. The preparation of α -acylamino ketones or these intermediates, however, requires a multi-step synthesis and/or the harsh reaction conditions. Although

the direct synthesis of oxazoles from simple ketones and nitriles with oxidants based on Tl(III) [14], Hg(II) [15], Fe(III) [16], or Cu(II) [17] have been developed as a convenient procedure, these procedures have met with the drawbacks including the limitation of the substrates and/or the use of toxic oxidants.

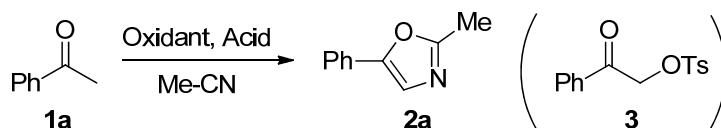
Hypervalent iodine(III) reagents have gained increasing popularity in organic syntheses due to their low toxicity, mild reactivity, high stability, easy handling, and so on [18]. Among them, [hydroxyl-(tosyloxy)iodo]benzene (Koser's reagent) and related reagents have been reported to work well for the α -sulfoxylations of ketones [19,20]. [Hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) has been used in the stepwise and one-pot synthesis of oxazoles via the formation of α -sulfonyloxy ketones as intermediate from simple ketones [21]. In addition, phenyliodine(III) diacetate (PIDA) with trifluoromethanesulfonic acid (TfOH) [22] or the iodoarene-oxone-TfOH system [23] efficiently promoted the direct synthesis of oxazoles from monocarbonyl compounds, such as alkyl aryl ketones with nitriles. To the best of our knowledge, however, there is no report about the direct synthesis of oxazoles from simple dicarbonyl compounds and nitriles [21,24,25]. As a part of our study on the iodine(III)-mediated synthesis of heterocycles [26,27], we carried out research on iodine(III) reagents for the direct synthesis of oxazoles from monocarbonyl or dicarbonyl compounds. In this article, we describe a single-step synthesis of highly substituted oxazoles by the reaction of ketones with nitriles in the presence of iodosobenzene (PhI=O) and a Brønsted acid.

2. Results and Discussion

2.1. Evaluation of Oxidants for the Direct Synthesis of Oxazole

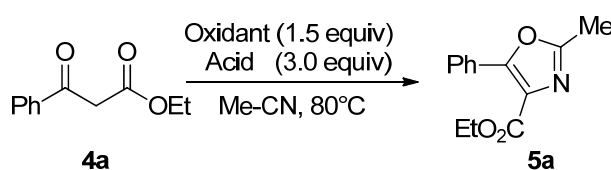
At the outset, we focused on the investigation of reactive oxidants for the reaction of monocarbonyl compounds with nitriles as shown in Table 1. In the presence of PIDA (1.2 equiv.) with TfOH (4.5 equiv.), the reaction of acetophenone (**1a**) in acetonitrile (MeCN) afforded the oxazole **2a** in 94% yield at 80 °C for 2 h (entry 1) [23], albeit low yield (22%) at ambient temperature for 3 h (entry 2). Exploring milder conditions, we examined the oxidants which were prepared from miscellaneous Brønsted acids (1.5–3.0 equiv.) and PhI=O (1.5 equiv.) [28,29], in the reaction of **1a** in MeCN (entries 3–8). Although the use of *p*-toluenesulfonic acid (TsOH) gave α -tosyloxy ketone **3** as a main product (entry 3), the other acids led to the desired formation of oxazole compound **2a** (entries 4–8). Thus, 3.0 equiv. TfOH showed the similar results to entry 1 (entry 7) and 3.0 equiv. bis(trifluoromethane-sulfonyl)imide (Tf₂NH) produced a good yield of **2a** (86%) after 3 h at ambient temperature (entry 9). It should be mentioned that the use of 10 equiv. of MeCN in 1,2-dichloroethane instead of MeCN solvent decreased the yield of **2a**, even under the similar conditions mediated by PhI=O with TfOH or Tf₂NH.

For the formation of oxazole **5a** from β -keto ester **4a** in MeCN, PhI=O/Tf₂NH system turned out to display superior activity to iodine(III) reagents/TfOH (Table 2). Thus, PhI=O (1.5 equiv.) with Tf₂NH (3.0 equiv.) improved the yield of **5a** to 51% at 80 °C for 16 h (entry 4), compared to the use of 1.5 equiv. PIDA or 1.5 equiv. PhI=O in the presence of TfOH (3.0–4.5 equiv.), in which **4a** were converted to **5a** in only 4–7% yields even at 80 °C for 24–25 h (entries 1 and 2). In the case of the extension of the reaction time (72 h) or the increase in the amount of Tf₂NH (6.0 equiv.), **5a** was obtained in 79–81% yields (entries 5 and 6).

Table 1. Evaluation of oxidants for the reaction of acetophenone (**1a**) in MeCN.

Entry	Oxidant (equiv)	Acid (equiv.)	Temp. (°C)	Time (h)	2a (%) ^[a]
1 ^[b]	PIDA (1.2)	TfOH (4.5)	80	2	94
2	PIDA (1.2)	TfOH (4.5)	rt	3	22
3	PhI=O (1.5)	TsOH (1.5)	80	18	- (3 69)
4	PhI=O (1.5)	HBF ₄ /Et ₂ O (1.5)	80	18	54
5	PhI=O (1.5)	TfOH (1.5)	80	18	69
6	PhI=O (1.5)	Tf ₂ O (1.5)	80	18	21 ^[c]
7	PhI=O (1.5)	TfOH (3.0)	80	3	94
8	PhI=O (1.5)	Tf ₂ NH (1.5)	80	3	40 (1a 16)
9	PhI=O (1.5)	Tf ₂ NH (3.0)	rt	3	86

^[a] Yields were determined by ¹H-NMR analysis; ^[b] Ref. [21]; ^[c] 2,4-Dimethyl-6-phenylpyrimidine was obtained in 38% yield.

Table 2. Evaluation of oxidants for the reaction of benzoylacetate **4a** in MeCN.

Entry	Oxidant	Acid	Time (h)	5a (%) ^[a]
1	PIDA	TfOH ^[b]	24	4
2	PhI=O	TfOH	25	7
3	PhI=O	TfOH	115	41
4	PhI=O	Tf ₂ NH	16	51
5	PhI=O	Tf ₂ NH	72	79
6	PhI=O	Tf ₂ NH ^[c]	3	81

^[a] Yields were determined by ¹H-NMR analysis; ^[b] TfOH: 4.5 equiv.; ^[c] TfOH: 6.0 equiv.

2.2. Scope of the Direct Synthesis of Oxazoles Using PhI=O with TfOH or Tf₂NH

The scope of monocarbonyl compounds **1** and dicarbonyl compounds **4** by means of the PhI=O (1.5 equiv.)-mediated procedure **A** (acid: 3.0 equiv. TfOH), **B** (acid: 3.0 equiv. Tf₂NH), or **C** (acid: 6.0 equiv. Tf₂NH) was shown in Tables 3 and 4 and Scheme 1. Procedure **A** could be applied to the reactions of monocarbonyl compounds **1a–g** in MeCN, and the corresponding oxazoles **2a–g** were obtained in 53–94% yields at 80 °C (Table 3, entries 1, 3–6, 8, and 9). Furthermore, procedure **B** brought about the formation of **2a** or **2e** at ambient temperature (entries 2 and 7). In the case of benzoylacetone (**1g**), an increase in the amount of Tf₂NH (procedure **C**) improved the yield of **5f** up to 69% at ambient temperature for 24 h (entry 11). Although the dicarbonyl compounds **4a,b** required the long time (72–139 h) to give good yields of products through procedure **B** (entries 12 and 14), procedure **C** reduced the reaction times (3 h) giving rise to **5a–c** in 67–83% yields (entries 13, 15 and 17). Bicyclic oxazole **5d** could be formed by procedure **C**, albeit in only 40% yield after 167 h

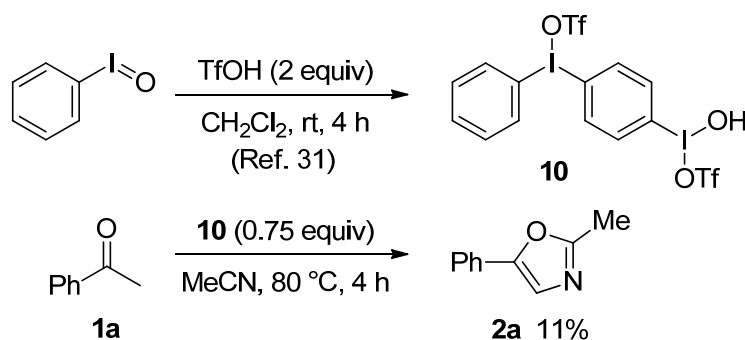
Table 4. The reactions of **4a–c** in EtCN or PhCN by the means of procedure C.

Entry	4	R ¹	R ²	R ³	(h)	2 or 5	Yield (%) ^[a]
1	4a	Ph	OEt	Et	2	8a	83
2	4a			Ph	3	9a	72
3	4b	Ph	Ph	Et	3	8b	89
4	4b			Ph	3	9b	67
5	4c	Me	Me	Et	20	8c	56
6	4c			Ph	20	9c	60

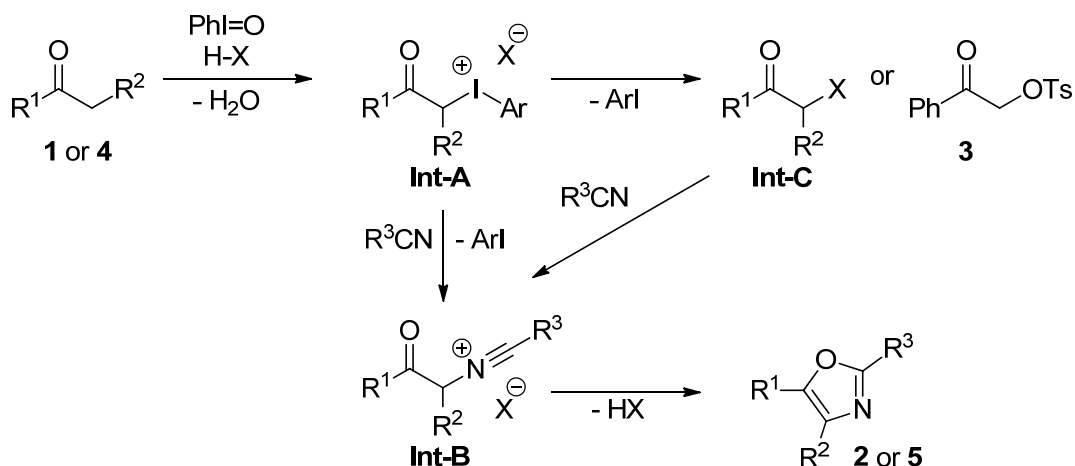
^[a] Isolated yields.

2.3. Mechanistic Considerations

Since it has been known that PhI=O reacts with two equiv. of TfOH in CH₂Cl₂ to produce the oxidant **10** [30], to better understand the present oxazole formation, we examined the reaction of acetophenone (**1a**) with **10** (Scheme 2). Thus, under conditions similar to those of entry 7 in Table 1, **1a** was treated with **10** (0.75 equiv.) instead of PhI=O (1.5 equiv.) and TfOH (3 equiv.) in MeCN to give **2a** in only 11% yield at 80 °C for 3 h. Therefore, **10** would not be considered to take part in the present oxazole formation.

Scheme 2. Preparation of **10** and the reaction of **1a** with **10**.

On the basis of abovementioned observations and the previous reports about the iodine(III)-mediated synthesis of oxazoles [21–23], the mechanism for the present oxazole formation from ketones **1** or **4** with nitriles as shown in Scheme 3 is proposed. That is, α -iodanyl ketone **Int-A**, which is generated from **1** or **4** with PhI=O and H-X (TfOH or Tf₂NH), would be converted to **Int-B** by the Ritter-type reaction with R³CN. **Int-C** generated by the reductive elimination of ArI might also be a possible intermediate for the formation of **Int-B**, and the subsequent cyclization of **Int-B** gives oxazoles **2** or **5**. The formation of **Int-A** and/or **Int-C** is supported by the formation of α -tosyloxy ketone **3** (69%) in the case of TsOH as an acid (Table 1, entry 3) [19,23].

Scheme 3. Proposed reaction mechanism of direct synthesis of oxazoles.

3. Experimental

3.1. General

All starting materials and reagents were commercially available. Dried organic solvents were purchased and used without further drying. Unless otherwise stated, all reactions were conducted under an argon atmosphere. Melting points were measured on a Yanaco SP-M1 melting point apparatus (Yanagimoto Co.) and were uncorrected. IR spectra were recorded on a HORIBA FT-710 FT-IR spectrometer. ^1H and ^{13}C -NMR spectra were measured in CDCl_3 with a Bruker AV300M FT NMR spectrometer at 300 and 75 MHz, and the chemical shifts are given in ppm using CHCl_3 (7.26 ppm) for ^1H -NMR and CDCl_3 (77.0 ppm) for ^{13}C -NMR as an internal standard, respectively. Mass spectra and HRMS were recorded by FAB method on a JMS-HX110 Mass spectrometer. Elemental analysis was measured on a Perkin-Elmer 240B or Elemental Vavio EL. For the TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Column chromatography was performed on Silica gel 60N (63–200 μm , Kanto Kagaku Co., Ltd.).

3.2. General Procedure for the Iodine(III)-Mediated Synthesis of Oxazoles

Ketone **1** or **4** (0.4 mmol) was added to a solution of iodosobenzene (132 mg, 0.6 mmol) and trifluoromethanesulfonic acid (106 μL , 1.2 mmol) or bis(trifluoromethanesulfonyl)imide (337 or 675 mg, 1.2 or 2.4 mmol), which were premixed in acetonitrile, propionitrile, or benzonitrile (2 mL) at 0 $^\circ\text{C}$ for 5 min, and the reaction mixture was stirred at ambient temperature or 80 $^\circ\text{C}$ until the consumption of substrate by TLC analysis. The mixture was diluted with ether and filtered through a short alumina column. After concentration of the filtrate to dryness, the subsequent purification gave the corresponding oxazole **2** or **5**. **2a** [21], **2c** [21], **2d** [31], **2e** [21], **6** [21], **7** [32], and **9a–c** [33] were identified by the comparison with ^1H -NMR spectra reported in the appropriate literature.

2-Methyl-5-(3'-methylphenyl)oxazole (2b). Colorless oil. IR (neat) ν cm^{-1} : 3054, 2925, 2863, 1610, 1560, 1519, 784, 748. ^1H -NMR (CDCl_3) δ 2.38 (s, 3H), 2.51 (s, 3H), 7.02(d, J = 7.6 Hz, 1H), 7.18 (s, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 9.2 Hz, 2H). ^{13}C -NMR (CDCl_3) δ 14.0, 21.4, 121.0,

121.6, 124.5, 128.0, 128.7, 128.9, 138.5, 151.2. FAB-LM m/z : 174.2 ($M^+ + H$). FAB-HM Calcd for $C_{11}H_{12}NO$: 174.0919, Found: 174.0906.

4-Chloro-2-methyl-5-phenyloxazole (2e). White solid. Mp 56 °C. IR (KBr) ν cm^{-1} : 3050, 3002, 2923, 2856, 1438, 1378. 1H -NMR ($CDCl_3$) δ 2.50 (s, 3H), 7.30–7.36 (m, 1H), 7.41–7.46 (m, 2H), 7.83–7.84 (m, 2H). ^{13}C -NMR ($CDCl_3$) δ 14.2, 124.8, 127.0, 128.7, 143.8, 159.4. FAB-LM m/z : 194.1 ($M^+ + H$). FAB-HM Calcd for $C_{10}H_9ClNO$: 194.0373, Found: 194.0383. Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.06; N, 7.23. Found: C, 62.21; H, 4.47; N, 7.23.

4-Cyano-2-methyl-5-phenyloxazole (2f). White solid. Mp 49 °C. IR (KBr) ν cm^{-1} : 3062, 2927, 2854, 2225. 1H -NMR ($CDCl_3$) δ 2.56 (s, 3H), 7.48–7.50 (m, 3H), 7.89–7.92 (m, 2H). ^{13}C -NMR ($CDCl_3$) δ 13.9, 108.0, 113.8, 125.2, 125.5, 129.3, 130.9, 157.8, 161.1. FAB-LM m/z : 185.2 ($M^+ + H$). Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.91; H, 4.39; N, 15.02.

4-Ethoxycarbonyl-2-methyl-5-phenyloxazole (5a). White solid. Mp 64 °C. IR (KBr) ν cm^{-1} : 3054, 3006, 2977, 2927, 2857, 1598, 1560, 1488. 1H -NMR ($CDCl_3$) δ 1.38 (t, $J = 7.1$ Hz, 3H), 2.54 (s, 3H), 4.40 (q, $J = 7.1$ Hz, 2H), 7.43–7.45 (m, 3H), 8.02–8.05 (m, 2H). ^{13}C -NMR ($CDCl_3$) δ : 13.9, 14.3, 61.3, 106.9, 127.1, 128.3, 128.3, 130.1, 155.3, 159.9, 162.2. FAB-LM m/z : 232.2 ($M^+ + H$). FAB-HM Calcd for $C_{13}H_{14}NO_3$: 232.0974, Found: 232.0977. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.80; H, 5.81; N, 5.89.

4-Benzoyl-2-methyl-5-phenyloxazole (5b). Colorless oil. IR (neat) ν cm^{-1} : 3031, 2965, 2927, 2856, 1710. 1H -NMR ($CDCl_3$) δ 2.58 (s, 3H), 7.40–7.47 (m, 5H), 7.47–7.55 (m, 1H), 7.95–7.98 (m, 2H), 8.05–8.08 (m, 2H). ^{13}C -NMR ($CDCl_3$) δ : 13.8, 127.3, 127.6, 128.1, 128.4, 130.0, 130.2, 132.9, 133.7, 137.5, 154.7, 159.0. FAB-LM m/z : 264.2 ($M^+ + H$). FAB-HM Calcd for $C_{18}H_{14}NO_2$: 264.1025, Found: 264.1014. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.38; H, 5.16; N, 5.40.

4-Acetyl-2,5-dimethyloxazole (5c). White solid. Mp 39 °C. IR (KBr) ν cm^{-1} : 1681. 1H -NMR ($CDCl_3$) δ 2.73 (s, 3H), 2.43 (s, 3H), 2.50 (s, 3H). ^{13}C -NMR ($CDCl_3$) δ 12.0, 13.6, 27.8, 134.5, 154.2, 158.4, 194.7. EI-LM m/z : 139.1 (M^+). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.02; H, 6.16; N, 9.82.

6,7-Dihydro-2-methylbenzo[d]oxazole-4(5H)-one (5d). Colorless oil. IR (neat) ν cm^{-1} : 2952, 2927, 2854, 1682. 1H -NMR ($CDCl_3$) δ 2.12–2.20 (m, 2H), 2.52 (s, 3H), 2.57 (t, $J = 5.9$ Hz, 2H), 2.81 (t, $J = 6.1$ Hz, 2H). ^{13}C -NMR ($CDCl_3$) δ 14.4, 23.2, 23.8, 38.0, 144.2, 156.1, 165.9, 185.8. FAB-HM Calcd for $C_8H_{10}NO_2$: 152.0712, Found: 152.0697.

4-Ethoxycarbonyl-2-ethyl-5-phenyloxazole (8a). White solid. Mp 37 °C. IR (KBr) ν cm^{-1} : 3066, 2983, 2933, 2875, 1714, 1240, 1189. 1H -NMR ($CDCl_3$) δ 1.38 (t, $J = 7.1$ Hz, 3H), 1.39 (t, $J = 7.6$ Hz, 3H), 2.88 (q, $J = 7.6$ Hz, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 7.42–7.47 (m, 3H), 8.01–8.04 (m, 2H). ^{13}C -NMR ($CDCl_3$) δ 11.2, 14.3, 21.6, 61.3, 126.7, 127.1, 128.3, 130.0, 155.0, 162.2, 164.1. FAB-LM m/z : 264.2 ($M^+ + H$). FAB-HM Calcd for $C_{14}H_{16}NO_3$: 264.1130, Found: 264.1126. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.79; H, 6.06; N, 5.61.

4-Benzoyl-2-ethyl-5-phenyloxazole (8b). Colorless oil. IR (neat) ν cm^{-1} ; 3064, 2981, 2937, 1656. $^1\text{H-NMR}$ (CDCl_3) δ 1.43 (t, $J = 7.6$ Hz, 3H), 2.92 (q, $J = 7.6$ Hz, 2H), 7.40–7.45 (m, 5H), 7.53–7.58 (m, 1H), 7.94–7.97 (m, 2H), 8.06–8.10 (m, 2H). $^{13}\text{C-NMR}$ (CDCl_3) δ 11.3, 21.7, 127.5, 127.7, 128.2, 128.5, 130.0, 130.4, 133.0, 133.7, 137.5, 154.5, 163.4. FAB-LM m/z : 278.2 ($\text{M}^+ + \text{H}$). FAB-HM Calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_2$: 278.1181, Found: 278.1177. Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.95; H, 5.42; N, 5.10.

4-Acetyl-2-ethyl-5-menyloxazole (8c). Colorless oil. IR (neat) ν cm^{-1} ; 1685. $^1\text{H-NMR}$ (CDCl_3) δ 1.25 (t, $J = 7.6$ Hz, 3H), 2.42 (s, 3H), 2.50 (s, 3H), 2.68 (q, $J = 7.6$ Hz, 2H). $^{13}\text{C-NMR}$ (CDCl_3) δ ; 11.1, 12.1, 21.4, 27.8, 134.4, 154.0, 162.7, 194.9. FAB-LM m/z : 154.1 ($\text{M}^+ + \text{H}$). FAB-HM Calcd for $\text{C}_8\text{H}_{12}\text{NO}_2$: 154.0868, Found: 154.0873.

3.3. Formation of α -Tosyloxy Ketone **3** under the Iodine(III)-Mediated Conditions

Ketone **1a** (47 μL , 0.4 mmol) was added to a solution of iodosobenzene (132 mg, 0.6 mmol) and *p*-toluenesulfonic acid monohydrate (114 mg, 0.6 mmol), which were premixed in MeCN (2 mL) at 0 $^\circ\text{C}$ for 5 min, and the reaction mixture was stirred at 80 $^\circ\text{C}$ for 18 h. The mixture was diluted with ether and filtered through a short alumina column. After concentration of the filtrate to dryness, the subsequent purification gave **3** (73.2 mg, 0.25 mmol, 63%). Compound **3** was identified by the comparison with the $^1\text{H-NMR}$ spectrum reported in the literature [20].

4. Conclusions

We have demonstrated the single-step synthesis of highly substituted oxazoles from ketones and nitriles by the use of iodosobenzene with trifluoromethanesulfonic acid or bis(trifluoromethanesulfonyl)imide. The present procedure could be applied not only to monocarbonyl compounds, but also to dicarbonyl ones. In particular, we believe that the reactivity of iodosobenzene with bis(trifluoromethanesulfonyl)imide sheds light on a new possibility for the use of hypervalent iodine compounds in organic synthesis.

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