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Iodine-mediated new strategy for the synthesis of 2,5-disubstituted oxazoles from methyl ketones and TosMIC

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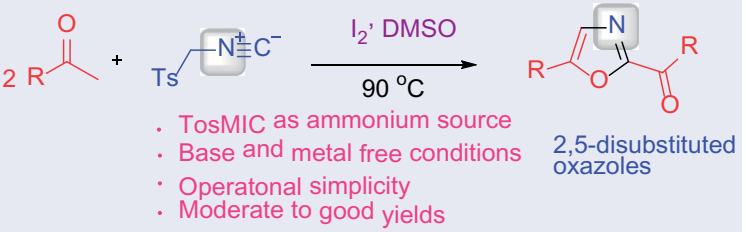
ABSTRACT

A new strategy has been developed for the construction of oxazoles from methyl ketones and TosMIC via self-sorting oxidative domino reaction strategy. In contrast to its usual reactivity as C–N≡C synthon in the synthesis of oxazoles, TosMIC was utilized as ammonium surrogate in the present method. The protocol is attractive in terms of readily available starting materials, metal and base free conditions, operational simplicity, C–N and C–O bond formation. A variety of 2,5-disubstituted oxazoles were prepared in moderate-to-good yields.

GRAPHICAL ABSTRACT



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KEYWORDS
2,5-Disubstituted oxazoles; metal and base free conditions; methyl ketones; self-sorting oxidative domino reaction; TosMIC

Introduction

Oxazoles are the important class of heterocycles found in biologically active molecules and natural products.[1,2] Owing to the remarkable medicinal potential and prevalence, a variety of methods has been developed to construct oxazole skeleton.[3,4] The [3 + 2] cycloaddition of α-acidic isocyanides to the molecules bearing C=O group is one of the most effective method for the synthesis of oxazoles.[5] Among them, *p*-toluenesulfonylmethyl isocyanide (TosMIC) based van Leusen oxazole synthesis is the well-known and most popular method.[6] There has been significant interest in the development and modification of van Leusen oxazole synthesis due to its pivotal role in organic synthesis.[7] Despite the efficiency and broad substrate scope, the requirement of stoichiometric amount of base and use of metal catalysts are the major drawbacks associated with these

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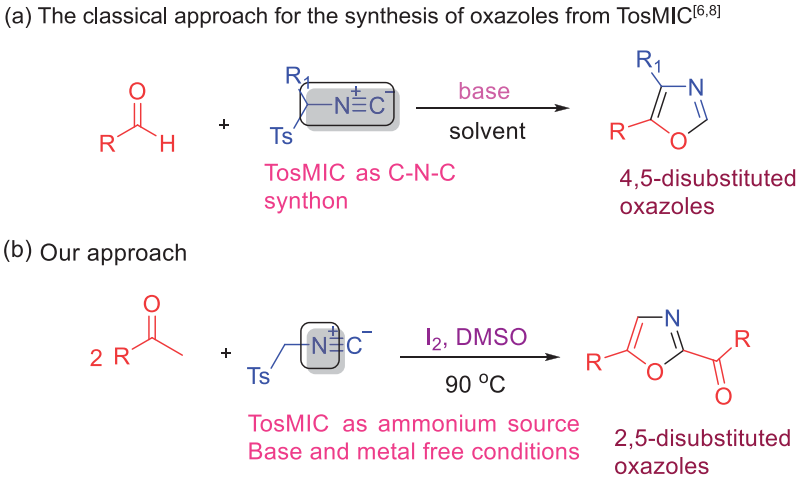
methods. Our group has a long-standing interest in diversification of synthetic utility of TosMIC.[8,9] Recently, we reported sulfono functionalization of alkenes, alkynes and their acid derivatives employing TosMIC as a sulfonylating agent.[10] Inspired by these results, we intended to probe the feasibility of the aldehydes and ketones with TosMIC by using I_2/DMSO as media. During the course of our investigation, serendipitously we found the formation of oxazoles when methyl ketones were used as substrates. Herein, we report a practical method for the synthesis of 2,5-disubstited oxazoles from methyl ketones and TosMIC utilizing an ecofriendly, nontoxic and cost-effective I_2/DMSO as a catalytic system (Scheme 1). Wu et al.[4f] presented iodine catalyzed synthesis of 2,5-disubstited oxazoles from methyl ketones and ammonium acetate. However, the present reaction is a valuable addition to explore the diversity of TosMIC and provides easy access to biologically significant 2,5-disubstited oxazoles.[4a,11] The conventional TosMIC-based strategy towards oxazoles is base mediated [3 + 2] cycloaddition reactions of methyl isocyanides with electrophilic acyl compounds. TosMIC as ammonium source to access oxazoles in contrast with classical methods in which TosMIC was employed as C–N≡C synthon, metal and base free conditions make the present reaction attractive for the construction of oxazole motif. Moreover, the current protocol delivers 2,5-disubstited oxazoles instead of 4,5-disubstited oxazoles the common products of van Leusen oxazole synthesis.

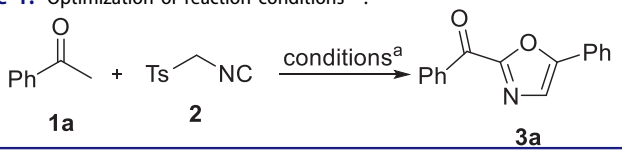
Results and discussions

We started with iodine-mediated reaction of acetophenone as a model substrate with TosMIC in DMSO at 90 °C. The reaction gave the product **3a**, determined as oxazole in 79% yield (Table 1, entry 1).[11a] The reactions with various isocyanides like ethyl isocyanoacetate, cyclohexyl isocyanide and *t*-butyl isocyanide failed to give the oxazole (only traces of the product was observed), attesting the unique reactivity of TosMIC as a privileged isocyanide (Table 1, entries 2–4). Next, we performed reactions with different iodine sources in order to find the suitable choice of catalyst. Nonetheless, the reactions



Scheme 1. The diversified role of TosMIC in the synthesis of oxazoles.

Table 1. Optimization of reaction conditions[a,b].



1a 2 3a

Entry	Isocyanide (equiv.)	Reagent (equiv.)	Temp (°C)	Time (h)	Yield (%)
1	TosMIC (1.0)	I_2 (1.5)	90	6	79
2	$EtOOCCH_2NC$ (1.0)	I_2 (1.5)	90	12	0
3	*t*-BuNC (1.0)	I_2 (1.5)	90	12	0
4	Cy-NC (1.0)	I_2 (1.5)	90	12	0
5	TosMIC (1.0)	NaI (1.5)	90	24	0
6	TosMIC (1.0)	KI (1.5)	90	24	0
7	TosMIC (1.0)	TBAI (1.5)	90	24	0
8	TosMIC (1.0)	NIS (1.5)	90	24	0
9	TosMIC (0.5)	I_2 (1.5)	90	6	78
10	TosMIC (0.5)	I_2 (1.0)	90	6	60

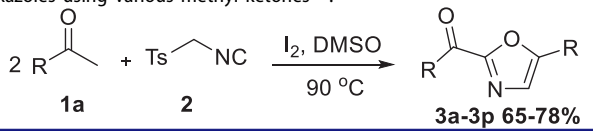
[a]Reaction conditions: **1a** (1.0 equiv.), TosMIC **2** (0.5 equiv.) and I_2 (1.5 equiv.) in DMSO.
[b]Yields refer to isolated products purified by column chromatography.

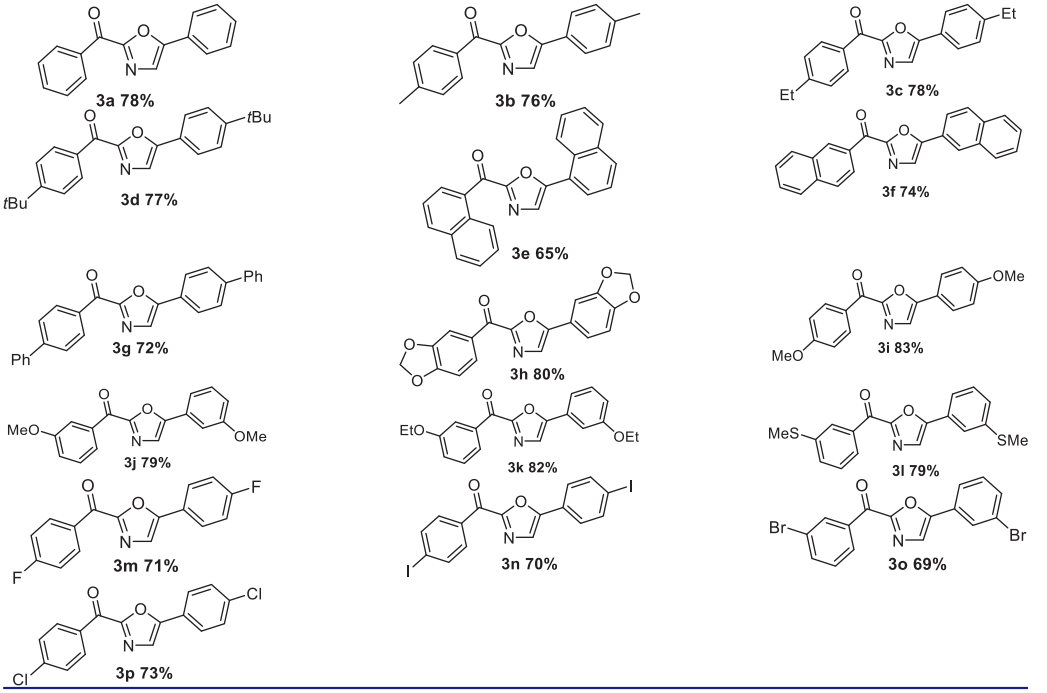
with KI, NaI, TBAI and NIS (Table 1, entries 5–8) failed to promote the reaction. We also tried the reaction with various solvents such as MeOH, CH_3CN and DMSO, but no desired product was formed. Taken together, iodine as a catalyst in DMSO medium was found to be suitable conditions to provide the desired product. After thorough study of reaction parameters (Table 1, entries 9–10), the optimal reaction conditions were obtained as follows: acetophenone (1.0 mmol), TosMIC (0.5 mmol), iodine (1.5 mmol), and DMSO (2 ml) at 90 °C for 6 h.

With this optimized reaction conditions in hand, we explored the scope of methyl ketones in the reaction. A variety of methyl ketones having different groups at various positions on the aromatic nucleus were subjected to react with TosMIC (Table 2). Pleasingly, the substrates with alkyl substituents such as methyl, ethyl, *t*-butyl (**1b–1d**) proceeded smoothly in this reaction to provide the corresponding oxazoles (**3b–3d**) in good yields. The sterically hindered 1-naphthyl methyl ketone **1e** and 2-naphthyl methyl ketone **1f** were successfully applied to the reaction conditions to give **3e** and **3f** in 65 and 74% yields, respectively. Acetophenone bearing phenyl group at para position **1g** provided **3g** in 72% yield. The acetophenones with electron donating groups such as 3,4-OCH_2O, OMe, OEt, SMe groups (**1h–1l**) performed well in the reaction to afford the (**3h–3l**) in 79–83% yields. The reaction scope was further tested with acetophenones bearing electron-withdrawing groups on aromatic ring, including fluoro, iodo, bromo and chloro groups (**1m–1p**). The reactions proceeded smoothly to furnish the desired oxazoles (**3m–3p**) in 69–73% yields. However, the reaction of acetophenones with strong electron withdrawing groups like cyano and nitro groups, ortho substituted acetophenones with groups like 2-OMe and 2,4-$(OMe)_2$ failed to give the expected oxazoles.

To get insights into the mechanism some control experiments were carried out (Scheme 2). The phenacyl iodide **1ab** and phenylglyoxal **1ac**, well-established intermediates of the methyl ketones under iodine/DMSO conditions,[12] gave the corresponding oxazoles in 73 and 71% yields, respectively (Scheme 2, Eq. a and b) . The

Table 2. Synthesis of oxazoles using various methyl ketones[a,b].





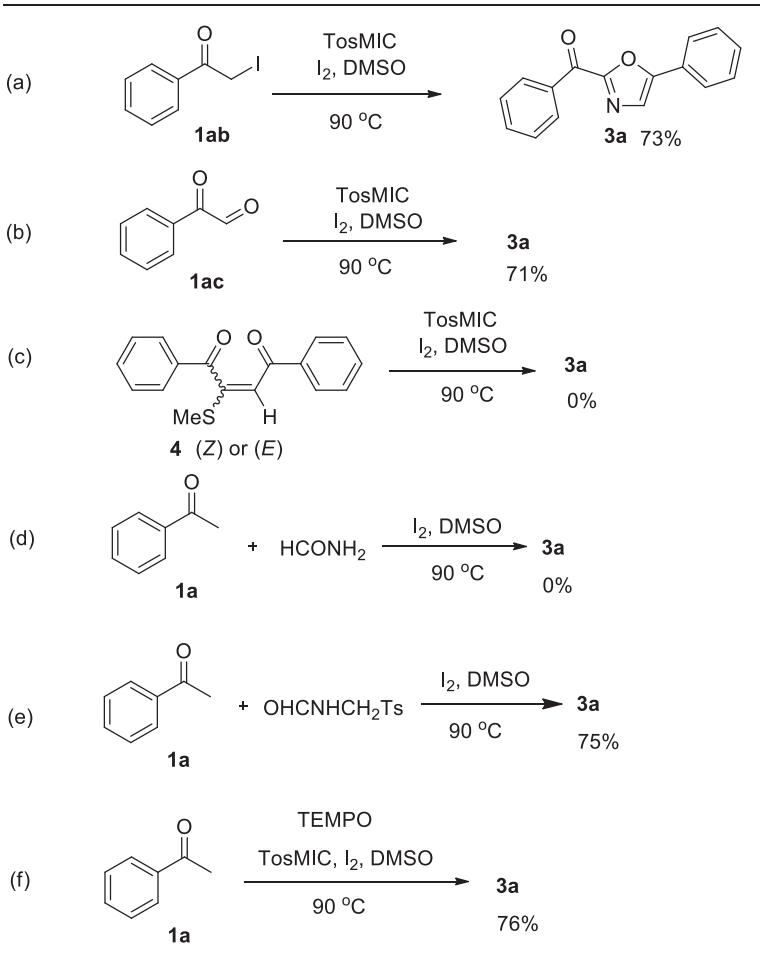
[a]Reaction conditions: acetophenone **1a** (1.0 equiv.), TosMIC **2** (0.5 equiv.) and I_2 (1.5 equiv.) in DMSO (2 mL) at 90 °C for 6 h.
[b]Yields refer to isolated products purified by column chromatography.

2-(methylthio)-1,4-diaryl-2-butene-1,4-dione **4**, the self-coupled product of acetophenone, did not provide the **3a** under standard conditions (Scheme 2, Eq. c). The reaction of acetophenone with formamide did not provide the oxazole (Scheme 2, Eq. d). When the reaction of hydrated TosMIC **5** was run under the standard conditions **3a** was obtained in 75% yield (Scheme 2, Eq. e). Further, the addition of TEMPO did not hamper the reaction, ruling out the possibility of a free radical mechanism (Scheme 2, Eq. e).

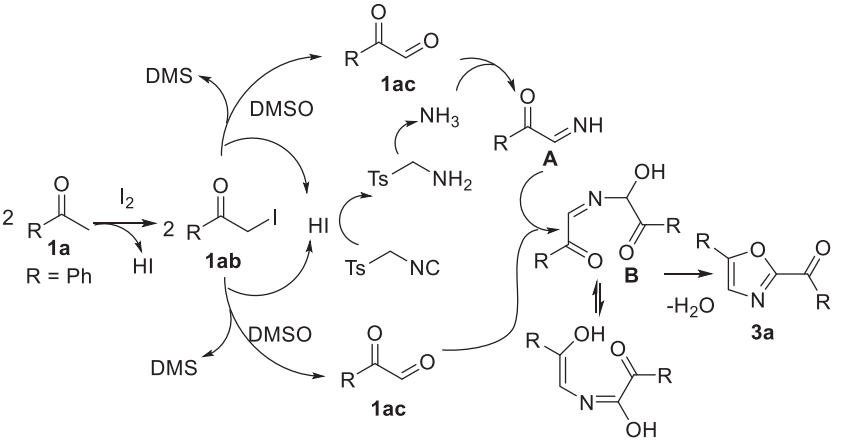
Based on these outcomes, the proposed mechanism for the formation of oxazoles is outlined in Scheme 3 using acetophenone as model substrate. Firstly, phenyl glyoxal **1ac** is generated by iodination and oxidation of methyl ketone **1a**. The phenylglyoxal thus generated reacts with ammonia formed *in situ* from TosMIC and HI[13] to afford intermediate **A**. Next, the formation of intermediate **B** takes place from **1ac** and **A**. The intramolecular nucleophilic reaction of **B** followed by dehydration gave the final product **3a**.

Conclusion

In conclusion, we have developed iodine-mediated novel strategy to construct oxazoles from methyl ketones and TosMIC via self-sorting oxidative domino reaction strategy. The



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

salient features of the current protocol are readily available starting materials, simple experimental procedure, C–N and C–O bond formation, employment of TosMIC as ammonium surrogate, the metal and base free conditions. The present methodology not only opens new horizons toward the synthesis of oxazoles, but also explores the diversity and versatility of TosMIC. The present methodology offers a new protocol for the synthesis of oxazoles and explore the versatility of TosMIC. Further studies towards the discovery and applications of the current method are currently underway in our laboratory.

Experimental

The chemicals used were obtained from Sigma-Aldrich (St. Louis, MO, USA) and used without further purification. All solvents were used as obtained from the commercial suppliers. ^{1}H NMR spectra were recorded at 400, and 500 MHz (using TMS as a reference), and ^{13}C NMR were recorded at 75 and 125 MHz (using the $CDCl_3$ triplet centered at δ 77.0 Hz as reference) in $CDCl_3$ as solvent at ambient temperature. Chemical shifts (δ) were recorded in ppm, coupling constants J were given in hertz (Hz), and multiplicity is reported as s (singlet), d (doublet), dd (doublet of doublet), td (triplet of doublet), t (triplet), m (multiplet), br. s, (broad singlet). IR spectra were recorded on at Perkin-Elmer IR-683 spectrophotometer with NaCl optics and are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system. High-Resolution Mass Spectra (HRMS) were performed on a high-resolution magnetic sector mass spectrometer. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units. All the reactions monitored by analytical thin-layer chromatography (TLC) using E-Merck silicagel plates (60G-254). All evaporations were carried out under reduced pressure on Büchi rotary evaporator at below 40 °C. All crude reaction products were purified by column chromatography silica gel (60–120 mesh) by using ethyl acetate and petroleum ether solvent system. Melting points were recorded on Büchi 535 melting point apparatus and are uncorrected.

General experimental procedure for synthesis of oxazoles

A mixture of acetophenone **1a** (0.12 g, 1.0 mmol), TosMIC **2** (0.09 g, 0.5 mmol) and iodine (0.38 g, 1.5 mmol) was stirred in DMSO (2 mL) at 90 °C for 6 h. After the reaction was complete, the mixture was quenched with a cold saturated aqueous $Na_2S_2O_3$ (2×20 mL) solution. Then the solution was extracted with EtOAc (2×20 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate =10:1) to provide **3a** as yellow solid, mp: 133–135 °C. Yield 78% (0.19 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50–8.46 (m, 2H), 7.86–7.82 (m, 2H), 7.65 (tt, J = 7.3, 2.2 Hz, 1H), 7.62 (s, 1H), 7.57–7.53 (m, 2H), 7.51–7.47 (m, 2H), 7.45–7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 157.0, 154.2, 135.3, 133.8, 130.7, 130.0, 129.1, 128.5, 126.7, 125.4, and 123.9; ESI-MS: 272 $[M+Na]^+$; HRMS: m/z calcd. for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0862; found: 250.0868.

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