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SHORT COMMUNICATION

Silver mediated one-step synthesis of oxazoles from α-haloketones

Christian Spiteri [a], Dougal J. Ritson [a], Amani Awaad [b], John E. Moses [a,b,*]

[a] *School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK*
[b] *Chemistry Department, Faculty of Sciences, King Saud University, Riyadh, Saudi Arabia*

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KEYWORDS

Oxazole;
α-Haloketo derivative;
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Abstract An efficient silver mediated one-step synthesis/construction of oxazoles using α-haloketones and primary amides is herein described. The methodology is efficient and simple to perform, giving the desired oxazoles in good to excellent yields.

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1. Introduction

The oxazole functional group is found in numerous bioactive natural products extracted from sources including bacteria and marine organisms (Wipf, 1995; Yeh, 2004). Their associated biological activities are extensive, including antifungal, antibacterial (Crank et al., 1973; Kaspady et al., 2009), antitubercular (Giddens et al., 2005) and anti-inflammatory properties (Crank and Foulis, 1971), making them attractive synthetic targets. Over the years, a number of methods have been devised for the synthesis of oxazoles (Turchi, 1981; Yeh, 2004). Classically, the Robinson–Gabriel synthesis was the most common route to oxazoles, which involves dehydration of 2-acylamino-ketones (Lister and Robinson, 1912). A versatile extension of this cyclodehydration reaction was developed by Wipf and Miller (1993), which involved either an oxidation followed by cyclodehydration or cyclodehydration of α-hydroxy amides with subsequent oxidation (Phillips et al., 2000) under mild conditions. Other efficient procedures include: (i) an iodine-catalysed tandem oxidative cyclization of aromatic aldehydes and 2-amino-1-phenylethanone hydrochloride derivatives (Wan et al., 2010); (ii) *t*-BuOOH/I_2-mediated domino oxidative cyclization of alkenes and benzylamine derivatives (Jiang et al., 2010); (iii) Lewis acid promoted reactions (Doyle et al., 1980) or a Rh-carbene insertion reaction (Shi et al., 2010) of diazocarbonyl compounds; (iv) copper(I)-catalysed cycloaddition of acyl azides and 1-alkynes (Cano et al., 2011) amongst others.

Another classic route to oxazoles is the Blümlein–Lewy method (BL) which involves the reaction of a primary amide and α-bromopyruvate in refluxing alcoholic media, giving the corresponding oxazoline, which then dehydrates to the oxazole product (Blümlein, 1884; Lewy, 1887). Although this is a useful method, the BL procedure is sometimes disadvantaged by the formation of undesirable by-products and low conversion of starting materials. We recently reported a one-pot modification of the Blümlein–Lewy oxazole method (BL) (Ritson et al., 2011), which provided a solution to these problems. In our method, the BL reaction was performed in 1,2-dichloroethane in the presence of silver(I) salts using microwave heating

* Corresponding author at: School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK. Tel.: +44 (0) 115 951 3533; fax: +44 (0) 115 95 13564.
E-mail address: john.moses@nottingham.ac.uk (J.E. Moses).

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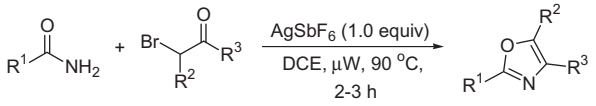


Scheme 1 Silver-mediated one-step synthesis of oxazoles.

(Scheme 1). The method was simple, efficient, high yielding and amenable to the synthesis of bisoxazoles, which are common motifs in macrocyclic natural products, such as (*R*)-telomestatin (Doi et al., 2006), (–)-disorazole C_1 (Wipf and Graham, 2004) and diazonamide A (Cheung et al., 2007). We now report further details on the substrate scope and tolerance of this methodology.

2. General experimental

Melting points were recorded using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. High Resolution Mass Spectra (HRMS) were recorded on VG micron Autospec or BrukermicroTOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin Elmer 1600 series or Bruker Tensor 27 spectrometer. NMR spectra were recorded at 400 and 100 MHz, for ^{1}H and ^{13}C NMR, respectively. Coupling constants are given in hertz (Hz), the shifts (δ) are given as parts per million (ppm) using tetramethylsilane as an internal standard. The following notations indicate the multiplicity of the signals: s (singlet), d (doublet) and m (multiplet). Column chromatography was performed using silica gel 60 (230–400 mesh). All reagents, chemicals and solvents were used as received from commercial suppliers. Microwave reactions were conducted on a CEM Discover Explorer microwave reactor in sealed tubes with stirring at a constant temperature for the indicated time.

2.1. General microwave procedure for oxazoles

The corresponding amide (0.3 mmol) and $AgSbF_6$ (1.0 equiv) were transferred in a dry 5 mL microwave vial, equipped with a magnetic stirrer and kept under Argon. Anhydrous 1,2-dichloroethane (0.45 mL) was added followed by α-haloketo derivatives (1.0 equiv). The resulting mixture was stirred for 5 min at ambient temperature and microwaved at 90 °C for 2 h under stirring conditions. After this time the reaction was cooled to ambient temperature, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the product was extracted with EtOAc (2 × 7 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was further purified by flash silica-gel chromatography using EtOAc and petroleum ether 40–60 °C.

2.2. 2-(4-Bromo-phenyl)-4-(4-methoxy-phenyl)-oxazole (*12*)

White solid: m.p. = 187–189 °C (chloroform); IR (neat, υ [cm^{-1}]) 1503, 1255; δ_H (400 MHz, $CDCl_3$) 7.99 (d, *J* 8.7 Hz, 2 H), 7.89 (s, 1 H), 7.75 (d, *J* 8.9 Hz, 2 H), 7.62 (d, *J* 8.7 Hz, 2 H), 6.98 (d, *J* 8.9, 2 H), 3.86 (s, 3 H); δ_C (100 MHz, $CDCl_3$) 160.9, 159.7, 142.0, 132.6, 132.0, 127.9, 126.9, 126.5, 124.8, 123.6, 114.2, 55.3; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{13}BrNO_2$, 330.0124; found 330.0112.

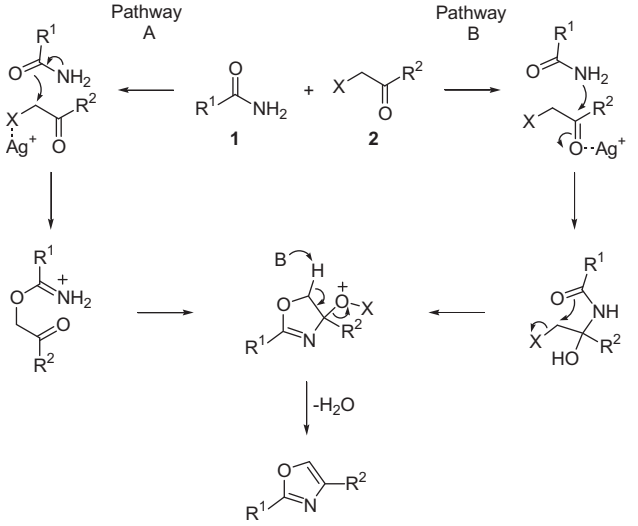
2.3. 2-(4-Bromo-phenyl)-4-(4-nitro-phenyl)-oxazole (*13*)

Yellow solid: m.p. = 195–196 °C (dichloromethane); IR (neat, υ [cm^{-1}]) 1609, 1508, 1346, 1078; δ_H (400 MHz, $CDCl_3$) 8.39 (d, *J* 9.1 Hz, 2 H), 8.31 (s, 1 H) 7.97–8.02 (m, 4 H), 7.65 (d, *J* 8.6 Hz, 2 H); δ_C (100 MHz, $CDCl_3$) 161.8, 147.4, 140.4, 137.2, 135.6, 132.2, 128.1, 126.1, 125.8, 125.5, 124.2; HRMS (ESI) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{10}BrN_2O_3$, 344.9869; found 344.9862.

3. Results and discussion

Our original conditions relied upon the reaction of primary amides with α-bromopyruvates in the presence of $AgSbF_6$ (Ritson et al., 2011). However, whilst the corresponding amide building blocks were readily available, the commercial availability of α-bromopyruvates is far more limited, thus placing restrictions on the accessibility of the substrates for this type of chemistry.

The dehydrative cyclization between the corresponding amide and α-bromopyruvate was proposed to occur via Ag^+ activation of the corresponding α-bromo group in **2** towards nucleophilic attack by the amide **1**, driven by the formation of the insoluble silver bromide salt (Scheme 2, pathway A). Although an alternative mechanism could be postulated, wherein the amide nitrogen first condensed with the activated carbonyl (Scheme 2, pathway B). In accordance with this mechanism (Scheme 2, pathway A), we considered that other α-haloketo derivatives could potentially be used as building blocks in our oxazoles' synthesis, thus providing an opportunity to expand the substrate scope of the reaction. The preparation of α-haloketo derivatives is well documented (for few examples see; Kowalski and Haque, 1985; VanBrunt et al., 2003; Graves et al., 2006; Moorthy et al., 2009) and numerous analogues are commercially available. Given the vast utility of oxazoles reported in literature (Turchi, 1981; Yeh, 2004), and the wide availability of α-haloketo derivatives, we sought to further delineate the utility and functional group tolerance of our silver-mediated oxazole synthesis. Accordingly, the α-halo acetophenone derivates **4**–**6** were used as test substrates, thus



Scheme 2 Mechanistic insight.

moving away from the pyruvate functionality. The synthesis of the α-chloride **5** and α-iodide **6** was achieved by mesylation of the hydroxyl of 2-hydroxyacetophenone (**9**), followed by nucleophilic displacement by the given halide.

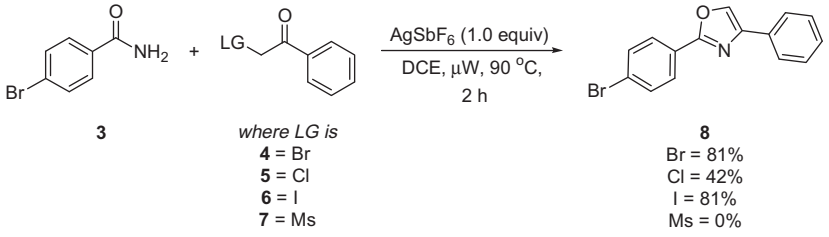
Our studies commenced with the reaction of 4-bromobenzamide (**3**, 1.0 equiv), 2-bromoacetophenone (**4**, 1.0 equiv) and $AgSbF_6$ (1.0 equiv) in 1,2-DCE for 2 h using our previously optimised conditions (Scheme 3) (Ritson et al., 2011). Gratifyingly, the target oxazole 2-(4-bromo-phenyl)-4-phenyl-oxazole (**8**) was obtained in 81% yield. Changing the leaving group to the chloride **5** afforded oxazole **8** in lower yield (42%), whilst with 2-iodoacetophenone (**6**), **8** was isolated in 81% yield.

In terms of reactivity, the α-chloroketo derivative **5** was significantly different compared to the corresponding α-bromo **4** and α-iodo **6** analogues. This contrasting reactivity can be explained by considering the heat of formation of the corresponding silver halogen salt and the carbon–halogen bond strengths. The heat of formation of AgCl, AgBr and AgI are −127, −100 and −63 kJ mol^{-1} (Atkins, 1998; Taylor et al., 1921), respectively; while the bond strengths for C–Cl, C–Br and C–I are 338, 276 and 238 kJ mol^{-1} (Atkins, 1998), respectively. Inspecting the enthalpic gain of forming the silver halide salts, one might expect **5** to give the highest yield then **4** and finally **6**. However, in relative terms forming AgCl is worth 27 kJ mol^{-1} more than forming AgBr but breaking the C–Cl bond costs 62 kJ mol^{-1} more than breaking the C–Br bond. On the other hand, forming AgBr provides 37 kJ mol^{-1} more than forming AgI but cleaving the C–Br bond costs 38 kJ mol^{-1} more than breaking the C–I bond. Hence, it is not surprising that **4** and **6** give identical yields and **5** is a far worse substrate in the reaction.

In order to further demonstrate the halophilic importance of silver(I) salts, the corresponding methanesulfonic acid 2-oxo-2-phenyl-ethyl ester (**7**) was prepared, which, unlike the haloketones, should not be significantly activated by silver. Interestingly, despite the mesyl group being an excellent leaving group, compound **7** failed to give 2-(4-bromo-phenyl)-4-phenyl-oxazole (**8**), even when used in excess (1.8 equivalence) or under prolonged microwave irradiation (6 h). In each case, **7** was fully recovered back from the reaction mixture. Since α-haloketo derivatives can be readily accessed from the corresponding mesylates, the selective activation of the corresponding haloketone by silver can, in principle, allow for the sequential construction of different oxazoles within the same molecule.

Although the current experiments do not fully ratify our proposed mechanism (pathway A, Scheme 2) they do help substantiate it. If pathway B (Scheme 2) were in operation, one would expect the mesylate **7** to be at least as an effective substrate as **5**, inasmuch as that once the condensation of **3** had taken place with **7**, the intramolecular displacement of MsO^- should be facile. On the contrary we observed no reaction between **3** and **7**. Further studies to resolve the mechanism are now underway.

Next, the substituent effects on the 2-bromoketo derivatives were investigated. Thus, 4-methoxyacetophenone (**10**), 4-nitroacetophenone (**11**) and 4-bromobenzamide (**3**) were used as test substrates (Scheme 4). When, 4-methoxyacetophenone (**10**, 1.0 equiv) was heated with 4-bromobenzamide (**3**, 1.0 equiv) in the presence of $AgSbF_6$ (1.0 equiv) in 1,2-DCE using microwave heating, the corresponding cycloadduct **12** was obtained in 65% yield. However, the reaction with 4-nitroacetophenone (**11**) was significantly slower, affording oxazole **13** in only 20% after 2 h. Increasing the reaction time to 5 h gave **13** in a significantly higher yield of 72%. As compared to the unsubstituted phenyl substrate **4**, the electron rich substrate **10** gave a slightly lower yield of oxazole product whereas the electron deficient substrate **11** gave a very low yield of the corresponding oxazole, after an equivalent reaction time. Considering these compounds are acting as electrophiles one would reasonably assume that **11** would be the better substrate, especially if pathway B (Scheme 2) was the correct mechanistic pathway. However, bearing in mind that aromatic nitro groups possess very weakly Lewis basic character, which would rule out deactivation of the Lewis acid, there may be dichotomous electronic behaviour of the electrophilic coupling

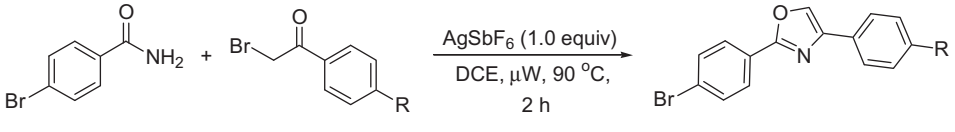


3

where LG is
4 = Br
5 = Cl
6 = I
7 = Ms

8
Br = 81%
Cl = 42%
I = 81%
Ms = 0%

Scheme 3 Substrate screening.



3

where R is
10 = OMe
11 = NO_2

where R is
12 = OMe = 67%
13 = NO_2 = 20%; after 5 h = 72%

Scheme 4 Investigating electronic effects of the α-bromoketone.

partner that accounts for the observed difference in reactivity. Also, the dehydration step is likely to be strongly affected by the electronic properties of the neighbouring aromatic group, and should also be considered as a factor to explain the difference in overall yield.

4. Conclusion

In conclusion, we have demonstrated that the substrate scope of our silver-mediated one-step synthesis of oxazoles can be extended to other commercially available α-haloketo derivatives. The methodology worked well with α-bromo or α-iodoketo derivatives, whereas lower yields were obtained with α-chloroketones. When the corresponding mesylate was employed, the reaction failed to yield any oxazole product, indicating the role of silver in activating the halo-group directly and thus supporting our proposed mechanism (pathway A, Scheme 2).

5. Conflict of Interest

The authors report no declarations of interest.

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