'On-water' synthesis of chromeno-isoxazoles mediated by [hydroxy(tosyloxy)iodo]benzene (HTIB)†

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Received 10th December 2009, Accepted 25th March 2010
First published as an Advance Article on the web 12th May 2010
DOI: 10.1039/b926085d

An efficient and handy method for the synthesis of chromeno-isoxazole/isoxazolines under 'on-water' conditions is described, together with a thorough mechanistic study.

Introduction

Isoxazoles and isoxazolines, two major classes of five-membered nitrogen heterocycles, are ubiquitous structural motifs that are found in a wide spectrum of organic molecules, some of which are biomedically important.[1] They have been used as building blocks in the synthesis of numerous natural products, and the procedures have been extensively documented in the literature. Their utility stems from their intrinsic properties, *i.e.*, selective ring opening to produce γ-amino alcohols, β-hydroxy ketones, β-hydroxy nitriles, β-hydroxy acids and esters and α,β- and β,γ-unsaturated ketones.[2] In particular, certain fused tricyclic derivatives comprised of isoxazoline/isoxazole and benzopyaran/naphthopyran units are known to possess multidrug functions (Fig. 1) with antidepressant, antipsychotic and antianxiolytic activities.[3] Apart from these, they are also used as synthetic precursors in the construction of various pharmaceutically useful compounds.[4]

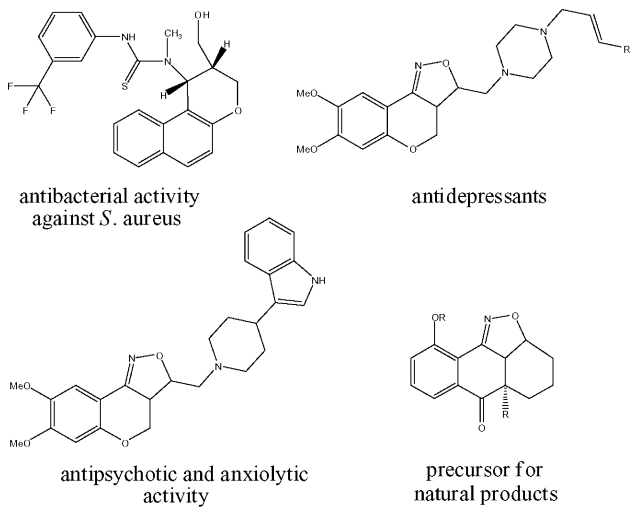

Fig. 1 Bioactive and synthetically important tricyclic isoxazoline molecules.

The *in situ* formation of a nitrile oxide and its intramolecular dipolar cycloaddition is one of the most extensively employed tools for the preparation of isoxazoline/isoxazole derivatives.[5] In this regard, like many other research groups around the world,[6] we have developed some synthetic routes to isoxazoles *via* the dehydration of nitroalkanes in the last few decades.[7] It is also noteworthy that a brief literature survey reveals that the dehydrohalogenation of hydroximoyl chlorides[8] and the oxidation of aldoximes[9] are also commonly used procedures for the generation of dipoles. In the synthesis of tricyclic isoxazoles, for example, the most frequently used reagent for oxidizing an aldoxime is NaOCl.[3,10] However, product yields using NaOCl reported by different groups are highly variable.[3,10] Magtrieve™, CAN, KI/I_2, DIB, PhIO/CTAB, $PhICl_2$, NCBT and chloramine-T are also oxidizing agents that can be used for the same purpose.[11,10b] Concerning the use of aqueous media, to our knowledge, only Hailes *et al.*[10d] (using NaOCl) and Maiti *et al.*[11d] (using PhIO/CTAB) have reported attempts to accomplish these goals. A limitation of the former method is that it requires a long time to complete a reaction and is applicable only to a limited number of examples. In the latter case, the reaction does not proceed in the absence of a cationic surfactant. In addition, these methods all involve the use of either toxic solvents, a complex combination of reagents or require a long reaction time. These facts prompted us to search for a better alternative.

In this context, from the viewpoint of cost, safety and environmental concerns, water is the most convenient solvent for synthetic purposes.[12] A plethora of chemical reactions in which water is used as the solvent have been described in the literature, even in cases where the substrate is insoluble in water. In particular, during the past few years, reactions of water-insoluble organic compounds that take place in aqueous suspensions ('on water') have received a great deal of attention because of their high efficiency and the straightforward synthetic protocols involved.[13] The advantages of conducting organic reactions 'on water' can be attributed to an enhancement in efficiency and rate, operational convenience and an improved safety profile owing to the excellent heat capacity of water.[14]

In a continuation of our ongoing project on the development of green synthetic protocols based on the 'on-water' concept,[15] we herein report our attempts to synthesize

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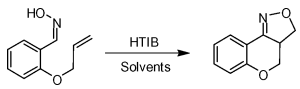
† Electronic supplementary information (ESI) available: Experimental information. CCDC reference numbers 751947, 751948, 751949 and 757190. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b926085d

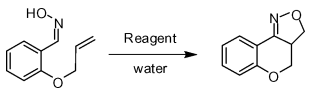
Table 1 Comparison of solvents[a]



Entry	Solvent	Yield (%)[b]
1	MeOH	91
2	DMF	90
3	CH_3CN	90
4	THF	89
5	H_2O	92
6	CH_2Cl_2	88
7	Toluene	79

[a] Using 1.1 equiv. HTIB. [b] NMR yield, using CH_2Br_2 as internal standard.

Table 2 Comparison of reagents



Entry	Reagent	Time (h)	Yield (%)[a]
1	CAN	3	27
2	Iodine	24	—
3	H_2O_2	24	—
4[b]	PhIO/CTAB	3	77
5	DIB	0.75	50
6	HTIB	0.75	79

[a] Isolated yields. [b] Ref. 11d.

tricyclic isoxazole derivatives under 'on-water' conditions using [hydroxy(tosyloxy)iodo]benzene (HTIB or Koser's reagent) as the oxidizing agent. The reason behind our choice of HTIB is that it is easy to handle, remarkably stable (with a long shelf-life) and has widespread synthetic applications that cover areas such as tosyloxylation, azidation, and hydroxylation,[16] the synthesis of heterocyclic compounds,[17] oxidative rearrangements and fragmentation,[18] and the oxidation of aldoximes, benzyl alcohols, glucals, sulfides and alkyl ketones.[19]

Results and discussion

In our initial studies, we focused our attention on optimizing the reaction conditions. Methanol was initially used as a solvent because both the substrate and reagent are methanol-soluble. In the first experiment, we used the simplest oxime, 2-(allyloxy)benzaldehyde oxime, and the product, 3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazole, was obtained in good (77%) yield. In a search of a better protocol, we carried out the same reaction using different solvents, and the yields were similar in all cases, except when toluene was used (Table 1). Given these circumstances, considering the advantages of using water as a solvent and its positive impact in the area of synthetic chemistry,[12,13,14] we examined the use of water as a solvent, and the results were found to be comparable to those using other solvents.

After choosing a suitable solvent, we examined a number of comparable or readily available oxidizing agents in aqueous media, in an attempt to identify a better alternative to HTIB.

No product was found when iodine or H_2O_2 were used as oxidants. On the other hand, the use of CAN resulted in a yield of only 27% of the expected product. We then used iodobenzenediacetate (DIB), but the product was obtained in only 50% yield. The results are shown in Table 2. All these results clearly point to the superiority of HTIB compared to other oxidizing agents in aqueous media.

Once a suitable solvent and reagent was selected, our next aim was to optimize the amount of reagent required for the reaction. We first concentrated on determining its catalytic efficiency. Using the same oxime and with a 10 mol% loading of HTIB, only a trace amount of the product was formed. An increase of the loading to 50 mol% resulted in a 35% yield of the expected product, and a trace amount of deoximination was observed. With a 1.1 equiv. of HTIB, the yield of the expected product reached a maximum, again with a minute amount of deoximination being observed. No further improvement in yields were observed with larger amounts of reagent. Hence we used 1.1 equiv. of HTIB in subsequent investigations.

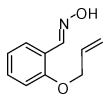
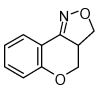
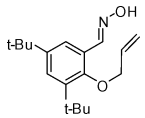
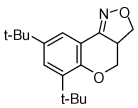
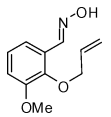
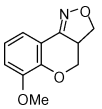
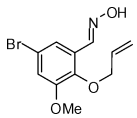
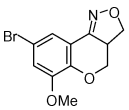
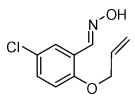
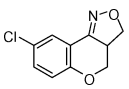
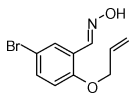
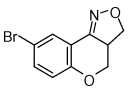
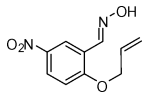
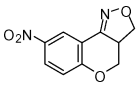
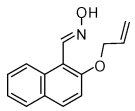
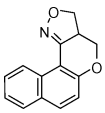
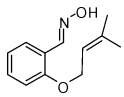
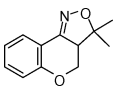
With the optimized conditions in hand, a wide range of substituted and unsubstituted 2-allyloxy/propargyloxy benzaldoximes were converted to their corresponding tricyclic isoxazoline derivatives in good to high yield. Evidence of the scope of this methodology with respect to various substituted 2-allyloxybenzaldoximes is shown in Table 3. The unsubstituted 2-allyloxybenzaldoxime and the substrates with electron-donating groups underwent smooth cyclisations to give tricyclic isoxazolines in high yields. However, moderate yields were obtained in case of chloro- and bromo-substituted 2-allyloxybenzaldoximes. Moreover, when the substrate contained a strongly electron-withdrawing group (NO_2), the yield was only 56%. A further interesting point to note is the extent of deoximination with respect to substitution on the benzene ring. In the case of the first four entries (entries **1–4**), the amount of deoximination product is less than 4%. It exceeded 4% in the case of the 5-Cl derivative (entry **5**) and reached 12% for the 5-Br derivative (entry **6**). On introducing a further electron-withdrawing group, such as a nitro group (entry **7**) extent of deoximination reached 30%.

The scope of this methodology was further investigated using branched 2-allyloxybenzaldoximes to better understand the stereochemical aspects of our methodology (Table 4).

The reactions of branched 2-allyloxybenzaldoximes also furnished moderate to excellent product yields. In particular, the presence of an acetate group resulted in high yields. The stereospecificity of the reactions was quite remarkable. Only one product was stereospecifically produced in almost all cases. NMR spectra showed the presence of a few extra peaks at higher field, due to the presence of another isomer, only in case of **10a** and **11a**. From the crystal structures of the products **14a**, **16a** and **17a** (Fig. 2), it can be seen that the addition is stereospecifically *syn*, which is consistent with a concerted [3+2] cycloaddition reaction in the final step. Less than 4% deoximination product was observed in all cases.

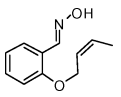
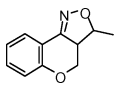
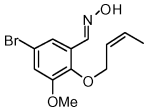
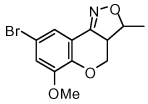
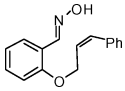
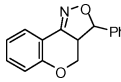
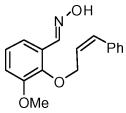
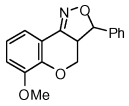
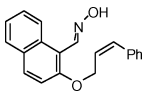
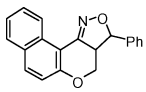
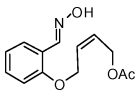
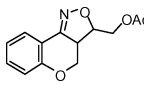
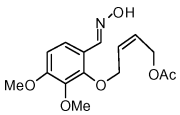
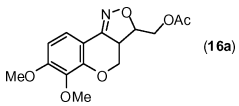
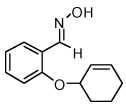
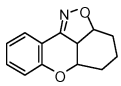
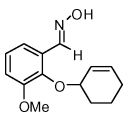
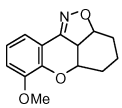
After successfully accomplishing the intramolecular cyclization of 2-allyloxy, branched 2-allyloxy and 2-cyclohexenyloxybenzaldoximes, we focused our attention on the synthesis of tricyclic isoxazole derivatives from

Table 3 HTIB-mediated synthesis of tricyclic isoxazoline derivatives under 'on-water' conditions[a]

Entry	Aldoxime	Product	Yield (%)[b]
1		 (**1a**)	79
2		 (**2a**)	85
3		 (**3a**)	85
4		 (**4a**)	86
5		 (**5a**)	80
6		 (**6a**)	56
7		 (**7a**)	50
8		 (**8a**)	79
9		 (**9a**)	81

[a] All the reactions were conducted on a 1 mmol scale. [b] Isolated yields.

Table 4 HTIB-mediated synthesis of tricyclic isoxazoline derivatives under 'on-water' conditions[a]

Entry	Aldoxime	Product	Yield (%)[b]
1		 (**10a**)	85
2		 (**11a**)	70
3		 (**12a**)	86
4		 (**13a**)	66
5		 (**14a**)	65
6		 (**15a**)	88
7		 (**16a**)	89
8		 (**17a**)	60
9		 (**18a**)	57

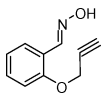
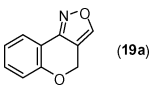
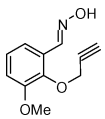
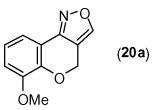
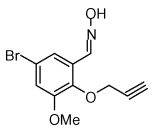
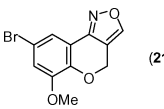
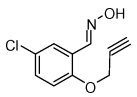
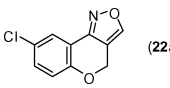
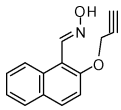
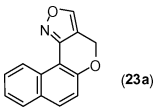
[a] All the reactions were conducted on a 1 mmol scale. [b] Isolated yields.

2-propargyloxybenzaldoximes. The results are shown in Table 5. As can be seen, unsubstituted as well as substituted 2-propargyloxybenzaldoximes underwent smooth cyclization to give the corresponding tricyclic isoxazole derivatives in good to excellent yields. Similar to the allyl derivatives, the presence of an electron-withdrawing group (**22a**) also results in a decreased yield. Interestingly, this method is also amenable to the synthesis of tetracyclic isoxazoles (**23a**). Similar to the data shown in Table 1, a very small amount of deoximination product (<3%) was observed in the cases of entries 1 to 3 in Table 5. The extent of deoximination is slightly higher in the case of 5-Cl (Table 5, entry 4).

To further extend the scope of our methodology, we applied the method to the synthesis of furopyrano-2-isoxazolines and furopyrano-2-isoxazoles, which are important precursor compounds in the synthesis of a number of useful compounds and catalysts.[20]

The substrates, **24** and **25**, were prepared by a 5-step process using literature procedures starting from diacetone glucose (Scheme 1). In the first step, diacetone glucose was alkylated by treatment with NaH and allyl/propargyl bromide in anhydrous THF.[21] The resulting allyl/propargyl diacetone glucose was treated with 2 N H_2SO_4 in methanol to selectively remove the isopropylidene group at the 1,2-position to obtain the corresponding diol.[22] Oxidative cleavage of the diol to the corresponding aldehyde was achieved by treatment with silica-supported $NaIO_4$ in dichloromethane.[23] The resulting aldehyde was further converted to the corresponding oxime (**24**, **25**) by treatment with $NH_2OH{\cdot}HCl$ and $NaHCO_3$ in ethanol at 70 °C. These allyl (**24**), and propargyloxime (**25**) derivatives were converted to furopyrano-2-isoxazoline (**24a**) and

Table 5 HTIB-mediated synthesis of tricyclic isoxazole derivatives under 'on-water' conditions[a]

Entry	Aldoxime	Product	Yield (%)[b]
1		 (**19a**)	88
2		 (**20a**)	74
3		 (**21a**)	89
4		 (**22a**)	72
5		 (**23a**)	69

[a] All the reactions were conducted on a 1 mmol scale. [b] Isolated yields.

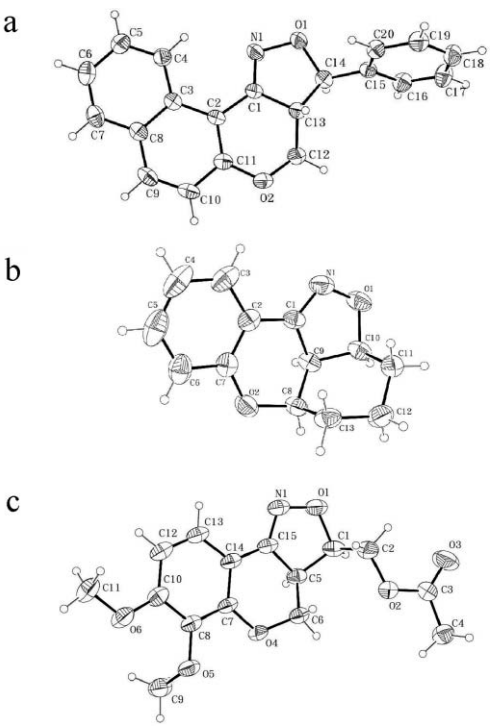
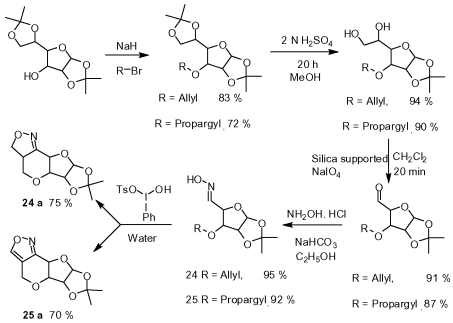


Fig. 2 Crystal structures of (a) **14a**, (b) **17a**, (c) **16a**.

furopyrano-2-isoxazole (**25a**) (Fig. 3) in good yield by the present method. It should be noted that the acid-sensitive isopropylidene group present in **24a** and **25a** remained intact. No trace of side-products were detected in the crude ^{1}H NMR spectrum, except for a very small amount of deoximination.



Scheme 1 Synthesis of furopyrano-2-isoxazoline and furopyrano-2-isoxazole.

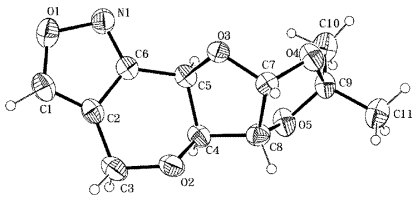


Fig. 3 Crystal structure of compound **25a**.

^{1}H NMR spectroscopy was used to gain further insights into the reaction. In this experiment the intensity of the initially formed PhI$^+$OH peak decreased with time and completely disappeared after 45 min. (Fig. 4). In an earlier report,

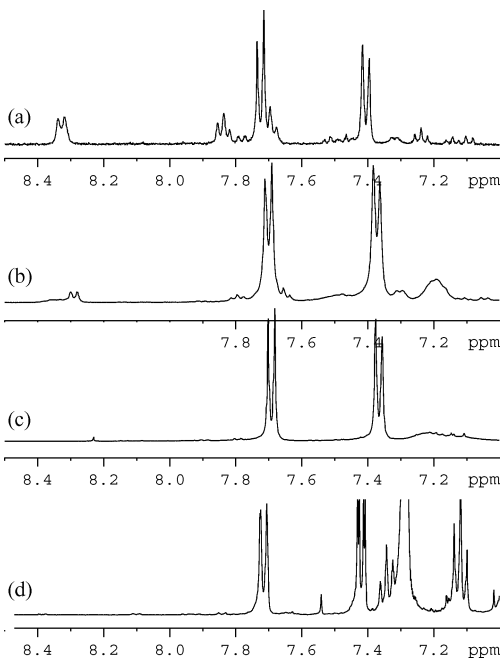
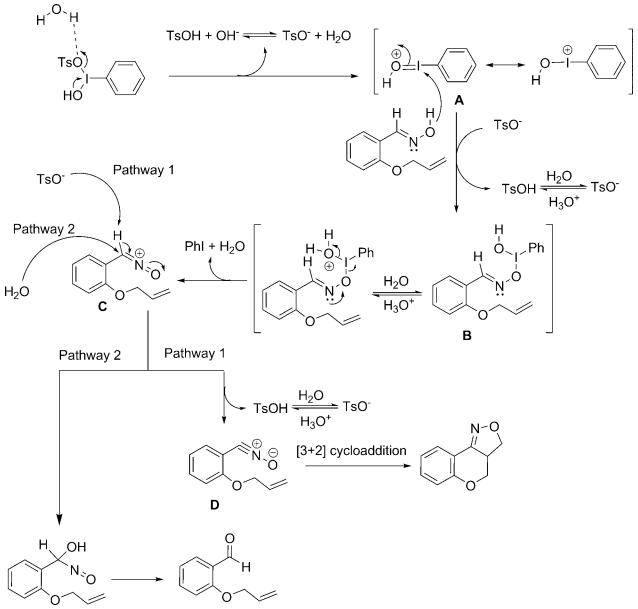


Fig. 4 Spectra related to the ^{1}H NMR experiment in D_2O. (a) Just after the addition of reagent to the starting material. The doublet at 8.31 ppm and the triplet at 7.85 ppm (assigned to PhI$^+$OH) appear. Another triplet, merged with the doublet for *p*-toluenesulfonic acid, appears at 7.70 ppm. Minor peaks are due to starting material. (b) 12 min after the start of the reaction. The PhI$^+$OH peak has decreased drastically. (c) 45 min after the start of the reaction. The PhI$^+$OH peaks have completely disappeared. (d) Spectra of the crude mixture after the ^{1}H NMR experiment, in $CDCl_3$. The doublet at 7.72 ppm, triplet at 7.32 and 7.12 ppm are assigned to iodobenzene. The doublet of doublets at 7.41 ppm corresponds to the product peak.

Ritcher and coworkers reported that HTIB ionises in aqueous solution (its solubility is 0.024 g ml^{-1})[24] to produce a (hydroxyl)phenyliodinium ion (PhI^+OH). This type of ionisation can be explained from the viewpoint of its structural feature,[25] *i.e.*, a weaker I–OTs bond is almost collinear with a stronger I–OH bond. The PhI^+OH formed in aqueous medium is probably stabilized by the delocalization of lone pair of oxygen electrons to the electron-deficient iodine centre, as shown in Scheme 2.



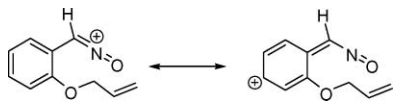
Scheme 2 Plausible route for the formation of isoxazoline derivatives.

Based on our ^{1}H NMR experiment and the previous studies,[24] we propose a mechanistic route for the formation a nitrile oxide under 'on-water' conditions (Scheme 2).

PhI^+OH (**A**) is the active oxidizing species. The logic behind this assumption is that the iodine center at PhI^+OH is less sterically demanding than HTIB. As a result, it enhances the efficiency of the reactions that start with nucleophilic attack at iodine. At this stage, the oxime, due to its high reactivity and its α-effect,[26] performs nucleophilic attack on the iodine centre of PhI^+OH resulting in the production of intermediate **B**. This, upon protonation, undergoes the elimination of water and iodobenzene and forms **C**. The abstraction of a proton from **C** by TsO^- produces a dipole, nitrile oxide, which undergoes further intramolecular cyclization to give the tricyclic isoxazoline or isoxazole. Although the medium and reaction conditions are different, the initial step of the mechanism appears to contradict the mechanism proposed by Maiti *et al.*,[11c] who predicted nucleophilic attack by the oxygen of iodosyl benzene, where our prediction is that the iodine center of the (hydroxyl)phenyliodonium ion (PhI^+OH) undergoes nucleophilic attack by the oxime oxygen. The nucleophilic attack of a water molecule on intermediate **C** is probably the reason behind the deoximination (Scheme 2). This mechanism is also different from that proposed by De *et al.*[27]

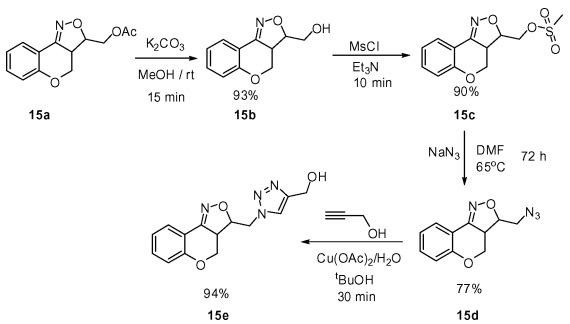
Our proposed mechanism accounts for the observations regarding deoximination. An electron-poor benzene ring promotes nucleophilic attack at the carbon of the CNO moiety of intermediate **C** and *vice versa*. Hence, an increase in the yield of deoximination product was observed with the introduction of an electron-withdrawing group (Table 3 and Table 5).

In order to defend this mechanism further, we can take into account the resonance structure of intermediate **C** (Scheme 3). This resonance decreases the electrophilicity of the carbon of the CNO moiety. The presence of an electron-withdrawing group lowers the efficiency of the resonance. A lower yield of deoximination indicates a larger amount of nitrile oxide formation. Hence, the presence of an electron-donating group at the benzene ring is expected to increase the yield of the desired isoxazoles (Table 3 and Table 5).



Scheme 3 Probable mechanistic routes for the deoximination.

To introduce more diversification, we considered the utility of triazole compounds in medicinal chemistry and the great interest of modern chemists in this field.[28] To the best of our knowledge, triazole derivatives of chrominoisoxazoles have not been explored to any extent. Our approach consists of four steps (Scheme 4). Deacetylation of compound **15a** with K_2CO_3[29c] followed by mesitylation[29a] gives compound **15c**. Heating **15c** at 60 °C with sodium azide in DMF[29a] produces **15d**, which is then amenable to a [3+2] cycloaddition with propargyl alcohol using 5 mol% $Cu(OAc)_2$ in water,[29b] producing the triazole **15e** in excellent yield. Further study of these types of triazole derivatives and the identification of biomedical applications is ongoing in our laboratory.



Scheme 4 The synthesis of (1-((3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazol-3-yl)methyl)-1*H*-1,2,3-triazol-4-yl)methanol.

Conclusions

In conclusion, we report a convenient and efficient method for the synthesis of tricyclic isoxazoline and isoxazole derivatives in good to excellent yields under 'on-water' conditions. Our methodology is equally applicable to preparing benzopyran-, naphthopyran- and even furopyrano-isoxazoles and -isoxazolines. A mechanism is proposed for the reaction based on ^{1}H NMR data, which is consistent with related observations from the literature. The reaction conditions are simple and the reagent used, HTIB, is stable in air and in the presence of moisture, readily available, and can be handled without any special care. Apart from these advantages, this

methodology is a milder, more environmentally friendly, and more cost-effective alternative to existing protocols.

Experimental

General procedure for oxidative [3+2] cycloaddition

To a 50 ml beaker containing oxime derivative (1 mmol) in 2 ml of water, small portions of [hydroxy(tosyloxy)iodo]benzene (1.1 mmol) were added with continuous stirring for a 45 min period. After the addition was complete, the stirring was continued for an additional 5 min. The crude product precipitated, isolated by filtration and washed with water. In the case of an oily product, the reaction mixture was quenched with sodium bicarbonate and the reaction mixture was extracted with ethyl acetate (2×10 mL). The organic layer was separated, dried over anhydrous sodium sulfate and concentrated to give the crude product. The crude product was passed through a short column to furnish the pure product.

Acknowledgements

We would like to express our sincere gratitude to the National Science Council of the Republic of China and National Taiwan Normal University for providing financial support to pursue this work. MJR is grateful to MOFA for a Taiwan Scholarship.

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