TRIFLIC ANHYDRIDE: A MILD REAGENT FOR HIGHLY EFFICIENT SYNTHESIS OF 1,2-BENZISOXAZOLES, ISOXAZOLO, AND ISOTHIAZOLO QUINOLINES WITHOUT ADDITIVE OR BASE

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GRAPHICAL ABSTRACT

Abstract The synthetic utility of trifluoromethanesulphonic anhydride (triflic anhydride, TA) without additive or base for the high-yielding synthesis of a wide variety of 1,2-benzisoxazoles from 2-hydroxyaryl aldoximes and ketoximes under mild conditions has been carried out for the first time. As a continuation of our study, syntheses of isoxazolo and isothiazolo quinolones have also been demonstrated using triflic anhydride under similar conditions. This method is simple and has benefits from the easy way to isolate the products in excellent yields.

Keywords Aldoximes; 1,2-benzisoxazoles; isothiazolo quinolones; isoxazolo quinolones; ketoximes; triflic anhydride

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INTRODUCTION

Because of their profound biological and pharmacological applications, 1,2-benzisoxazoles are useful intermediates in medicinal chemistry.[1–6] In view of their extensive biological and pharmacological applications, many synthetic methods have been developed to construct these nitrogen–oxygen heterocycles,[7] such as cycloaddition of benzenes and nitrile oxides,[8] copper-catalyzed cyclization of Z-oximes,[9] and the reaction of hydroxylamine-o-sulfonic acid with 2-hydroxyphenyl carbonyl compounds.[10] In the past decade, many catalysts have also been developed for the synthesis of 1,2-benzisoxazoles, which includes the base-catalyzed cyclization of 2-hydroxyaryl aldoximes and ketoximes with Ac₂O,[11,12] SOCl₂,[13] Ga(OTf)₃,[14] Ph₃P,[15] and trichloroacetyl isocyanate.[16] Although some benefits are there for each of the reported methods, the limitations and drawbacks associated with the synthesis of 1,2-benzisoxazoles in these reports,[17,18] directed us to find a new and simple way of accessing the target molecules.

Generally, many benzo/hetero fused isoxazole derivatives and isothiazole derivatives exhibit a wide variety of pharmacological properties, as the structural units of many molecules consisting of 1,2-benzisoxazole moiety.[20] In particular, isothiazolo quinolines are known to possess antibacterial activity.[21] A number of methods are available in the literature for the synthesis of these heterocycles because of their great synthetic and medicinal importance.[22–26] However, triflic anhydride–mediated simple synthesis of isoxazolo and isothiazolo quinolines without additive or base has not been reported yet. Recently, we have demonstrated the synthesis of simple 1,2-benzisoxazole by the utility of N-triflylimidazole, an in situ–generated reagent by the reaction of triflic anhydride and imidazole,[19] which prompted us to synthesize a series of such compounds in the absence of imidazole. Hence, in continuation of our work on the use of triflic anhydride (TA), we now report the synthesis of 1,2-benzisoxazoles, isoxazolo quinolines, and isothiazolo quinolines under mild and neutral reaction conditions at room temperature without the formation of any side products.

RESULTS AND DISCUSSION

To optimize the reaction conditions such as temperature, solvent, and amount of reagent, and to study the feasibility of TA-mediated synthesis of 1,2-benzisoxazoles, the cyclization of salicylaldoxime to its corresponding 1,2-benzisoxazole (Scheme 1) was selected as a model.

The reaction was carried out at room temperature with equivalent amount of TA in dichloromethane (DCM). Addition of the TA produced the corresponding 1,2-benzisoxazole at rt in moderate yield in 4 h (Table 1, entry 1). The successful synthesis of 1,2-benzisoxazole derivatives via the cyclization of different aldoximes

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\text{Scheme 1. Synthesis of 1,2-benzisoxazole (1) from salicylaldoxime using TA.}
\]
Table 1. Synthesis of 1,2-benzisoxazoles using TA

| Entry | Compound | Substrate | Product | Time (h) | Isolated yield\(^a\) (%) |
|-------|----------|-----------|---------|----------|--------------------------|
| 1     | 1        | ![Structure](image1) | ![Structure](image2) | 4        | 72                       |
| 2     | 2        | ![Structure](image3) | ![Structure](image4) | 3        | 93                       |
| 3     | 3        | ![Structure](image5) | ![Structure](image6) | 3        | 90                       |
| 4     | 4        | ![Structure](image7) | ![Structure](image8) | 3        | 88                       |
| 5     | 5        | ![Structure](image9) | ![Structure](image10) | 5        | 97                       |
| 6     | 6        | ![Structure](image11) | ![Structure](image12) | 4        | 90                       |
| 7     | 7        | ![Structure](image13) | ![Structure](image14) | 4        | 86                       |
| 8     | 8        | ![Structure](image15) | ![Structure](image16) | 3        | 91 (88\(^b\))           |
| 9     | 9        | ![Structure](image17) | ![Structure](image18) | 3        | 86 (82\(^b\))           |
| 10    | 10       | ![Structure](image19) | ![Structure](image20) | 2        | 85                       |

(Continued)
prompted us to investigate the applicability of this procedure for the generation of other 1,2-benzisoxazoles via the cyclization of variety of ketoximes (Scheme 2).

A similar trend of reaction was observed in the cyclization of oxime of 2-hydroxyacetophenone to the corresponding 1,2-benzisoxazoles (Table 1, entry 5). The reaction was completed in 5 h at rt with 96% isolated yield. Thus, the cyclization of a wide range of structurally varied 2-hydroxyarylaldoximes and ketoximes in the presence of TA was carried out under the optimized reaction conditions described previously. The results (Table 1) show that a variety of structurally varied 2-hydroxyarylaldoximes and ketoximes cyclized smoothly in DCM to give the corresponding 1,2-benzisoxazoles in excellent yield (82% to 96%) and purity.

To evaluate the reactivity of the system with another solvent, we also carried out the reaction using ethylene dichloride (EDC). With EDC, in two different experiments the cyclization was completed in 3 h at rt with 88 and 82% yields (Table 1, entries 8 and 9 respectively) and almost the same results were obtained at 80°C. Because the results obtained with EDC in terms of reaction time and isolated yield were not so encouraging in comparison with those of DCM and because EDC is potentially carcinogenic (cat. 1B), we thought to demonstrate the cyclization in DCM. As shown in Table 1, the use of this method at room temperature and under

| Entry | Compound | Substrate | Product | Time (h) | Isolated yielda (%) |
|-------|----------|-----------|---------|---------|---------------------|
| 11    | 11       | ![Substrate Image] | ![Product Image] | 2       | 83                  |
| 12    | 12       | ![Substrate Image] | ![Product Image] | 4       | 94                  |

*Isolated yields of pure products.

bThe reaction was carried out in EDC.

Scheme 2. Synthesis of various substituted 1,2-benzisoxazoles (1–12) from 2-hydroxyarylaldoximes and ketoximes using TA.
neutral conditions gave 83 to 94% yields of various substituted 1,2-benzisoxazoles (Table 1, entries 6, 7, and 10–12).

In view of the synthetic importance of isoxazolo and isothiazolo quinolines, and as a continuation of this work, we have also demonstrated the synthesis of a variety of isoxazolo and isothiazolo quinolines via the cyclization of variety of substituted oximes of 2-chloro-3-formylquinoline and 2-mercapto-3-formylquinoline in the presence of TA (Scheme 3).

Under the present optimized reaction conditions, a comparatively long reaction time was observed with substrates such as the oximes of 2-chloro-3-formyl-7-methoxy-quinolin and 2-chloro-3-formyl-7-methyl-quinolin (Table 2, entries 3 and

Scheme 3. Synthesis of various substituted isoxazolo and isothiazoloquinoines (13–19) using TA.

| Entry | Compound | Substrate | Product | Time (h) | Isolated yield\(^a\) (%) |
|-------|----------|-----------|---------|----------|------------------------|
| 1     | 13       | ![Image](image1) | ![Image](image2) | 6         | 84                     |
| 2     | 14       | ![Image](image3) | ![Image](image4) | 6         | 92                     |
| 3     | 15       | ![Image](image5) | ![Image](image6) | 8         | 84 (80\(^b\))         |
| 4     | 16       | ![Image](image7) | ![Image](image8) | 7         | 84 (78\(^b\))         |
| 5     | 17       | ![Image](image9) | ![Image](image10) | 6         | 74                     |
| 6     | 18       | ![Image](image11) | ![Image](image12) | 5         | 85                     |
| 7     | 19       | ![Image](image13) | ![Image](image14) | 5         | 90                     |

\(^a\)Isolated yields of pure products.
\(^b\)The reaction was carried out in EDC.
4 respectively). Nevertheless, all the oximes of quinoline are cyclized in 5 to 8 h with excellent yields of 74 to 92%. In comparison with the observed yield of various products as depicted in Table 2, excellent yields of products are obtained when the oximes of 2-chloro-3-formyl-4-methyl quinoline (Table 2, entry 2) and 2-mercapto-3-formyl-7-methyl quinoline (Table 2, entry 7) are subjected to cyclization.

The plausible mechanism of formation of various 1,2-benzisoxazoles is depicted in Schemes 4–6. The initial step is the reaction between phenolic OH and Tf$_2$O, which is favored because of high nucleophilicity of phenolic OH and facile cleavage of the S-O bond. The resulting phenyl trifluoromethyl sulfonate acts as a better leaving group and facilitates an intramolecular ipso attack by the oxime hydroxyl group, leading to the expulsion trifluoromethane sulfonic acid and the formation of 1,2-benzisoxazole 1 (Scheme 4).

In the reaction of 2-chloroquinoline-3-aldoxime, the oxime forms a trifluoromethane sulfonate, which again brings intramolecular ipso chloro displacement at C-2 of quinoline by the expulsion of trifluoromethane sulfonylchloride, leading to the formation of isoxazole-fused quinoline (13) (Scheme 5). Similar structurally analogous intramolecular reactions have been observed in the formation of pyrazoloquinolines.[28]

In the reaction of 2-mercaptoquinoline-3-aldoximes, the free oxime acts as a better nucleophile than the tautomeric thiol. The oxime has now been converted into a better leaving group. The N-S bond formation is triggered by the deprotonation at the ring N and the nucleophilic attack on the azomethine nitrogen. The N-S bond formation is facilitates by the facile cleavage of the N-O bond with the loss of

![Scheme 4. Plausible mechanism of formation of 1,2-benzisoxazole (1) using TA.](image)

![Scheme 5. Plausible mechanism of formation of isoxazoloquinoline (13) using TA.](image)
trifluoromethane sulfonet moiety, leading to the formation of isothiazole fused quinolines (17) (Scheme 6).

The common features in this reaction seem to be the formation of O-trifluoromethanesulfonate and the leaving ability favoring the formation of O-C and S-N bonds by an intramolecular ipso SN-Ar pathway.

**EXPERIMENTAL**

The reagents employed were high-purity commercial samples, which were used as received from vendors without further purification. Reactions were carried out in an oven-dried round-bottom flask. Column chromatography was performed on silica gel (200–400 mesh). Thin-layer chromatography (TLC) was performed on alumina silica gel 60F254 (Fischer) detected by ultraviolet (UV) light (254 nm) and iodine vapors. The melting points were determined by open capillaries on a Buchi apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Nicolet-Impact-410 FT-IR spectrometer, using KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC-300F 300-MHz, spectrometer in dimethylsulfoxide (DMSO-$d_6$) using tetramethylsilane (TMS) as an internal standard with $^1$H resonance frequency of 300 MHz and $^{13}$C resonance frequency of 75 MHz. Gas chromatographic (GC) analyses were performed on an Nucon 5700 series gas chromatograph. GC-MS analyses were performed on a Shimadzu 2010 series mass selective detector instrument. Elemental analysis was carried out by using Heraeus CHN rapid analyzer. All the compounds gave C, H, and N analysis within $\pm 0.4\%$ of the theoretical values. Dry DCM and EDC were obtained from commercial sources by the standard procedure.[27]

**Typical Procedure for the Synthesis of 1,2-Benzoxazoles Using Triflic Anhydride**

The desired 2-hydroxaryl aldoxime or ketoxime (2.0 mmol) in 5 mL dry DCM was taken in an oven-dried round-bottom flask. To the reaction mixture was added dropwise triflic anhydride (2.0 mmol) in DCM under nitrogen for 15 min. The reaction mixture was stirred at rt and the progress of the reaction was monitored by TLC.
and GC-MS (Table 1). After completion of reaction, the contents were poured on to crushed ice (100 mL), neutralized with 10% NaHCO₃ solution (20 mL), and extracted with DCM (3 × 15 mL). The pure products were obtained by column chromatography with hexane–ethyl acetate mixture (80:20). All the 1,2-benzisoxazole derivatives were characterized by GC-MS, ¹H and ¹³C NMR, and elemental analysis, and the results are compared with authentic samples.

Supporting Information

Full experimental details, IR, ¹H and ¹³C NMR spectra, and elemental analysis can be found via the “Supplementary Content” section of this article’s Web page.

CONCLUSIONS

In conclusion, we have successfully demonstrated the mild, convenient method for the synthesis of a wide variety of 1,2-benzisoxazoles, from 2-hydroxyaryl aldoximes and ketoximes using triflic anhydride. Further we have also demonstrated the synthesis of different substituted isoxazolo and isothiazolo quinolines using triflic anhydride at room temperature. This practical and simple method led to good yields with high purity of 1,2-benzisoxazoles under mild conditions without addition of external base or additive. This protocol could serve as a valuable alternative to the known reaction systems.

Further work, including the development of synthetic applications of aryl and heteroaryl oximes and exploration of the enormous potential of triflic anhydride as a triflyl source in organic synthesis, is under way in our laboratory.

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