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A fast and efficient bromination of isoxazoles and pyrazoles by microwave irradiation

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Abstract—A fast and efficient method has been developed for the bromination of isoxazoles and pyrazoles using microwave irradiation. In this method, *N*-bromosuccinimide was used in different acid solvents according to the reactivity of the substrates to give mono-brominated isoxazoles and pyrazoles in good yields. Trifluoroacetic acid was found to be the best solvent for highly unreactive isoxazoles and pyrazoles.

1. Introduction

Isoxazole and pyrazole derivatives are interesting heterocyclic compounds since they show a wide range of pharmacological properties including anti-inflammatory,[1] anti-cancer,[2] anti-bacterial,[3] anti-viral,[4] anti-diabetic,[5] antimicrobial, and antifungal activities.[6] Some isoxazoles and pyrazoles display agrochemical properties (i.e., herbicidal and soil fungicidal activity) and have applications as pesticides and insecticides.[7] Brominated isoxazoles and pyrazoles are useful synthetic intermediates capable of undergoing transition-metal-catalyzed cross-coupling reactions, such as Heck, Stille, Suzuki, Sonogashira, and Negishi couplings.[8] There is an obvious demand for brominated isoxazoles and pyrazoles due to their importance both as synthetic intermediates and as pharmacological targets. A number of methods have been described previously for the halogenation of isoxazoles and pyrazoles.[9] Stephens and co-workers described a methodology for the bromination of 3,5-diarylisoxazoles using *N*-bromosuccinimide (NBS) in acetic acid.[9a] But for deactivated isoxazoles, such as 5-phenyl-isoxazole-3-carboxylate, especially with electron withdrawing substituents on the 5-phenyl ring, the known bromination methods proved to be unsatisfactory, giving only traces of the brominated products. Our search of the literature showed no precedent for the direct bromination of 5-phenyl-isoxazole-3-carboxylate. This type of 4-haloisoxazole has been synthesized by thermolysis of 2-halo-2H-azirines or haloazidoalkenes,[10] which required multi-step synthesis to get the 4-halo products.

Microwave heating has been widely used for many organic reactions, including Diels–Alder, esterification, etherification, oxidation, hydrolysis, cyclization, Claisen, Reformatsky, Knoevenagel, and metal-catalyzed couplings.[11] Although microwave induced bromination has been used for bromination of activated aromatics or heteroaromatics,[12a] α-bromination of carbonyl compounds[12b] and side chain bromination of methyl aromatic compounds,[12c] no report exists on microwave induced bromination of non-activated heteroaromatics, such as isoxazoles and pyrazoles.

In this Letter, we report a new, rapid, and efficient method for the bromination of isoxazoles and pyrazoles via microwave irradiation. With this method, the C-4 position of isoxazoles and pyrazoles can be selectively brominated in good yield. In addition, we also describe the iodination of isoxazoles and pyrazoles by *N*-iodosuccinimide (NIS) under similar conditions.

2. Bromination of the isoxazoles

The reactivity of the C-4 position of the isoxazole ring is sensitive to the electronic properties of its neighboring substituents.[9a] Electron withdrawing groups on the C-3 or C-5 position of isoxazoles deactivate electrophilic bromination on the C-4 position. When we used existing

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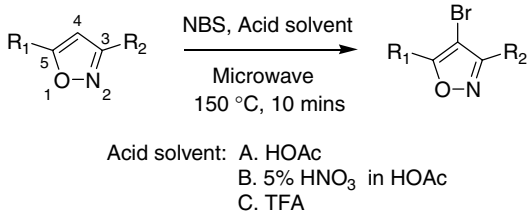
bromination methods for these deactivated isoxazoles, we observed little or no products even after prolonged heating. As NBS has shown enhanced activity in acidic solvents, we attempted to brominate these unreactive isoxazoles using NBS in different acid solvents via microwave irradiation.

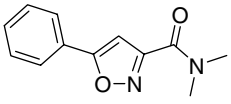
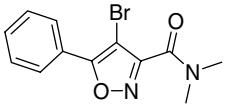
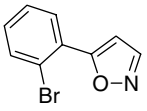
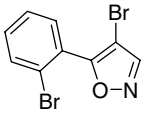
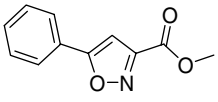
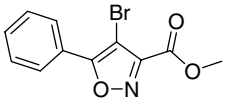
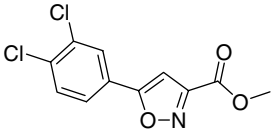
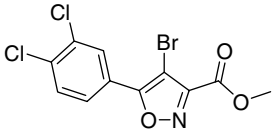
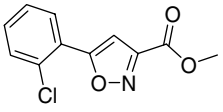
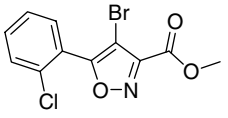
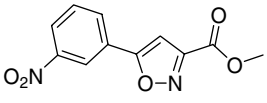
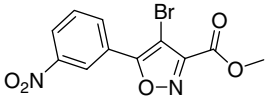
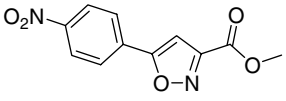
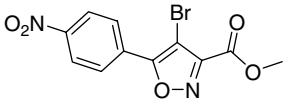
To determine the optimal acidic solvent for the bromination of isoxazoles, a series of isoxazoles were studied under microwave irradiation. For each isoxazole, we used three different acid solvents: acetic acid, 5% fuming nitric acid in acetic acid, or trifluoroacetic acid (Scheme 1). The bromination conditions which gave the best yields for each isoxazole are shown in Table 1. The reactions were performed using 50–100 mg of starting isoxazoles and 1.2 equiv of NBS.[13] The starting 5-phenylisoxazole-3-carboxylates were prepared by cyclization of 2,4-dioxo-4-phenylbutanoate with hydroxylamine hydrochloride.[14] The bromination reaction has been scaled up to gram quantities using 30-ml size microwave vessels.



Scheme 1. Bromination of isoxazoles.

N,*N*-Dimethyl-5-phenylisoxazole-3-carboxamide was brominated readily by a mixture of NBS in acetic acid with the formation of the mono-brominated product (Table 1, entry 1). Deactivated isoxazoles (Table 1, entries 2–5) required more acidic conditions and the use of 5% fuming nitric acid in acetic acid. Bromination of methyl 5-(2-Cl–phenyl)isoxazole-3-carboxylate (Table 1, entry 5) was relatively slow and needed an extended reaction time (45 min) to be completely brominated. Trifluoroacetic acid was especially suitable for highly unreactive compounds (Table 1, entries 6 and 7), which have *m*- or *p*-NO_2 groups on the 5-phenyl ring. Most of these

Table 1. Bromination of isozazoles using NBS under microwave irradiation

Entry	Substrate	Product	Method[a]	Yield[b] (%)
1			A	87
2			B	84
3			B	84
4			B	88
5			B[c]	80
6			C	90
7			C	81

[a] Reaction conditions: microwave heating at 150 °C for 10 min or as otherwise indicated. Method A. HOAc as solvent; Method B. 5% HNO_3 in HOAc as solvent; Method C. TFA as solvent.
[b] Yields of isolated products.
[c] Microwave heating at 150 °C for 45 min.

reactions were completed within 10 min under microwave irradiation. The yields for brominated isoxazoles varied from 80% to 90% (Table 1). Traditional heating in an oil bath using the same acid solvents also gave satisfactory yields but required much longer reaction time. For example, 5-(3-nitro-phenyl)isoxazole-3-carboxylate (substrate in Table 1, entry 6) was heated at reflux with NBS in TFA for 24 h to give the mono-brominated product in 82% yield.[15]

The structure of methyl 4-bromo-5-phenylisoxazole-3-carboxylate (Table 1, entry 3) was confirmed by single crystal X-ray crystallography (Fig. 1).[16] The phenyl and isoxazole rings have an intersecting angle of 20.8°.

To compare the reactivity and selectivity of the bromination conditions, three isoxazoles were examined as shown in Table 2. All the reactions were heated under microwave irradiation at 150 °C for 10 min. The mole ratio of starting material/brominated product/bis-brominated product was determined after separation of the reaction mixture. For bromination of 5-(2-bromophenyl)isoxazole (Table 2, entry 1), heating in acetic acid provided 66% conversion of the starting material. With the addition of 5% fuming nitric acid to acetic acid, the reaction went to completion after heating for 10 min. However, when trifluoroacetic acid was used as solvent, the product was accompanied by 15% of bis-brominated byproduct. The second Br was added to the phenyl ring based on the NMR data.[17] For 5-(4-nitrophenyl)-isoxazole-3-carboxylic acid methyl ester (Table 2, entry 3), heating in acetic acid gave no brominated product while trifluoroacetic acid as solvent provided complete bromination after 10 min. No bis-brominated product was observed in this reaction. While trifluoroacetic acid as solvent greatly increased the reactivity of isoxazoles, acetic acid or 5% fuming nitric acid in acetic acid provided better selectivity for mono-bromination.

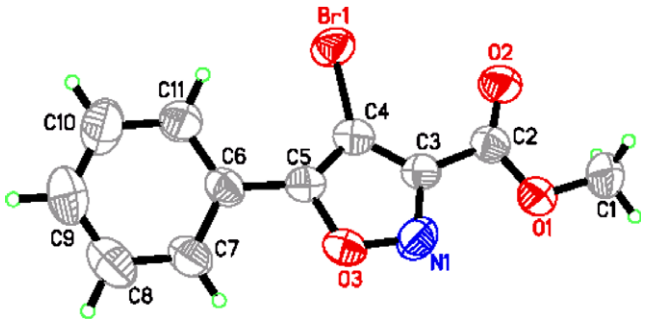
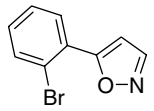
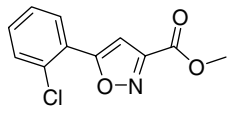
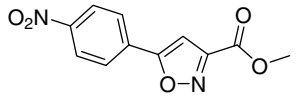


Figure 1. X-ray structure of methyl 4-bromo-5-phenylisoxazole-3-carboxylate.

Table 2. Comparison of different acid solvents for bromination of isoxazoles

Entry	Substrate	Method[a]	SM/Br-product/bis-Br-product
1		A	34/66/0
		B	0/100/0
		C	0/85/15
2		A	100/0/0
		B	52/48/0
		C	0/87/13
3		A	100/0/0
		B	44/56/0
		C	0/100/0

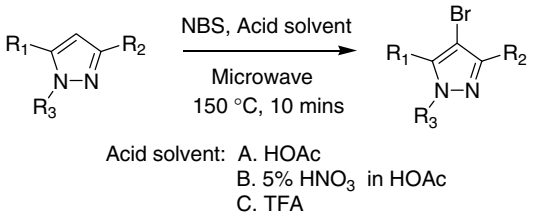
[a] Reaction conditions: microwave heating with 1.5 equiv NBS at 150 °C for 10 min. Method A. HOAc as solvent; Method B. 5% HNO_3 in HOAc as solvent; Method C. TFA as solvent.

3. Bromination of pyrazoles

The microwave assisted bromination method was also applied to pyrazoles (Scheme 2). As shown in Table 3, pyrazoles were brominated using NBS in different acid solvents, with yields ranging from 78% to 91% (Table 3). As observed in the isoxazole case, the use of a stronger acid was required for unreactive pyrazoles.

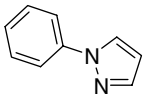
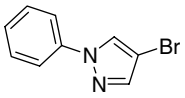
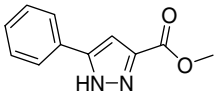
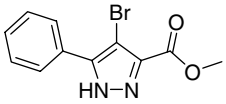
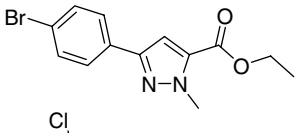
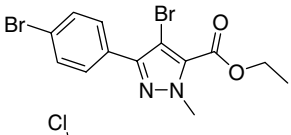
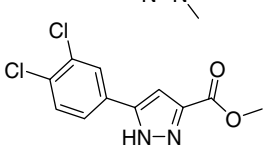
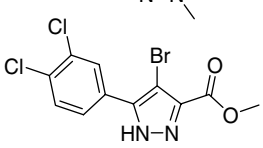
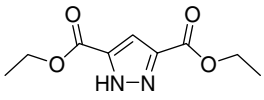
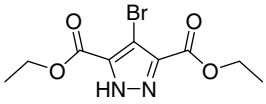
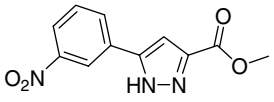
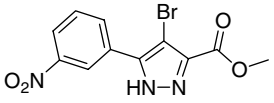
Following the successful demonstration of the bromination of isoxazoles and pyrazoles, we proceeded to extend the generality of the reaction conditions to iodination using NIS. Two examples are shown in Scheme 3. The reactions afforded the desired mono-iodinated products in good yields.

In conclusion, we have developed a fast and efficient method for the bromination of isoxazoles and pyrazoles employing NBS in acid solvents under microwave irradiation conditions. Trifluoroacetic acid as solvent was shown to be an effective and useful solvent for the bromination of very unreactive heteroaromatics. This procedure offers several advantages, providing enhanced yields, shorter reaction times, and operational simplicity. Iodination of isoxazoles and pyrazoles was also achieved by this method in good yields. This method has provided simple and convenient synthesis of bromo-intermediates which can be further transformed to aryl, vinyl, and alkynyl-substituted isoxazoles and pyrazoles via Suzuki, Stille, and Heck coupling reactions. This bromination method is under investigation for further application to other aromatic or heteroaromatic compounds.

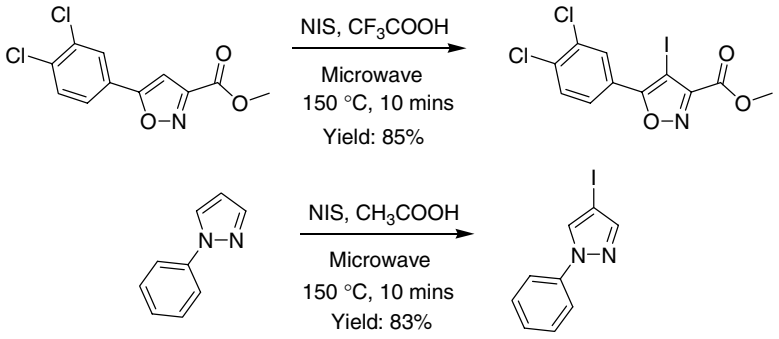


Scheme 2. Bromination of pyrazoles.

Table 3. Bromination of pyrazoles using NBS under microwave irradiation

Entry	Substrate	Product	Method[a]	Yield[b] (%)
1			A	84
2			A	89
3			A	91
4			B	83
5			B	88
6			C[c]	78

[a] Reaction conditions: microwave heating at 150 °C for 10 min or otherwise indicated. Method A. HOAc as solvent; Method B. 5% HNO_3 in HOAc as solvent; Method C. TFA as solvent.
[b] Yields of isolated products.
[c] Microwave heating at 130 °C for 10 min.



Scheme 3. Iodination.

Acknowledgments

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Supplementary data

Experimental procedures, spectroscopic data for all new compounds, selected ^{1}H and ^{13}C NMR spectra, structure determination of the bis-brominated byproduct 4-bromo-5-(2,5-dibromophenyl)isoxazole and X-ray crystallography data for 4-bromo-5-phenylisoxazole-3-carboxylate. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.118.

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13. *Typical procedure for bromination:* Preparation of methyl 4-bromo-5-phenyl-isoxazole-3-carboxylate (Table 1, entry 2). In a 10 ml glass microwave vessel were placed methyl 5-phenylisoxazole-3-carboxylate (61 mg, 0.3 mmol), NBS (64 mg, 0.36 mmol), and 2 ml of 5% fuming nitric acid in HOAc. The reaction mixture was heated at 150 °C for 10 min under microwave irradiation using a *Emrys™ Optimizer*. After completion of the reaction, as indicated by LCMS, the solvent was removed and the residue was purified by flash chromatography to give the product in 84% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.02 (3H, s), 7.51–7.54 (3H, m), 8.05–8.07 (2H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 53.2, 89.8, 126.0, 127.2, 129.1, 131.3, 154.6, 159.4, 167.6. HRMS (M+H) Calcd for $C_{11}H_9NO_3Br$: 281.9766. Found: 281.9758.
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15. This traditional heating reaction was performed by refluxing under N_2, which can be used for large scale synthesis.
16. Methyl 4-bromo-5-phenylisoxazole-3-carboxylate is a known compound in the literature (Ref. 10). Since our ^{13}C NMR of this compound does not match the NMR data in Ref. 10, we obtained X-ray crystallography data to confirm the structure of this compound. Crystallographic data for methyl 4-bromo-5-phenylisoxazole-3-carboxylate has been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 642296.
17. When trifluoroacetic acid was used as solvent, the bromination of 5-(2-bromophenyl)-isoxazole gave some bis-brominated byproduct 4-bromo-5-(2,5-dibromophenyl)isoxazole. The structure of the bis-brominated byproduct was determined based on 1D ^{1}H NMR and 2D HMBC NMR data.