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# Synthesis of Alkyl Aryl(heteroaryl)acetates from *N*-Oxides, 1,1-Difluorostyrenes, and Alcohols

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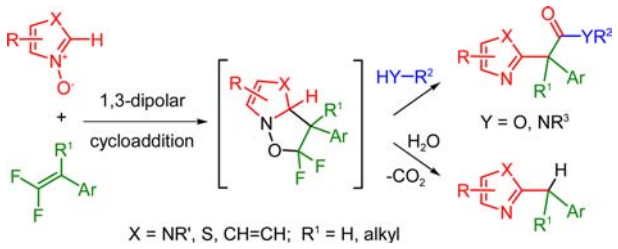
## ABSTRACT




**Derivatives of aryl(heteroaryl)acetic acids or aryl(heteroaryl)methanes are formed from imidazole or thiazole *N*-oxide, 1,1-difluorostyrene, and an alcohol, amine, or water in a three-component reaction, which probably occurs via 1,3-dipolar cycloaddition. The whole process is a novel method for functionalization of a heterocyclic ring in a position originally occupied by hydrogen. Preliminary experiments show that it occurs for 6-membered *N*-oxides as well.**

Highly functionalized azines and azoles are of great practical importance,[1] in particular as pharmaceuticals,[2] ligands,[3] and catalysts.[4] In their synthesis, replacement of hydrogen in the heteroaromatic ring seems particularly attractive, as it avoids preparation of prefunctionalized substrates. In this regard, aromatic *N*-oxides[5] have been recognized for a long time as valuable substrates for C−H functionalization in *cine* and *tele*[6] and other types[7] of nucleophilic substitutions of hydrogen, as well as metalation[1c] and transition metal catalyzed reactions developed in recent years by Fagnou[8] and others.[9] Radical processes (e.g., the Minisci reaction) are also of some importance.[10]

1,3-Dipolar cycloaddition of aromatic *N*-oxides and *N*-acylated or *N*-tosylated pyridinium imides has been extensively used for the construction of new heterocyclic

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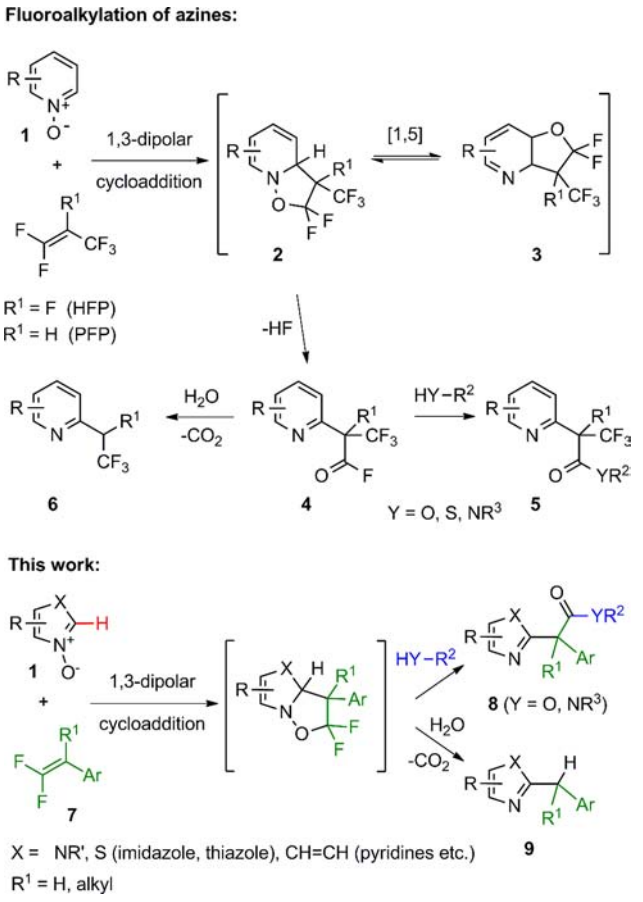
**Scheme 1.** 1,3-Dipolar Cycloaddition of *N*-Oxides and Fluoroalkenes



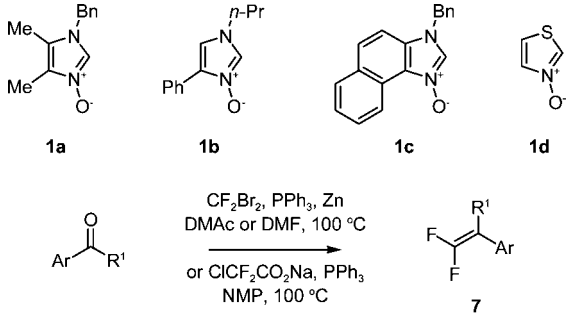

systems.[11] However, it has not been often employed as a method of functionalization of the aromatic ring. Substitution of hydrogen at C-2 has been observed as a result of cycloaddition (concerted or stepwise) with such dipolarophiles as electron poor alkynes,[12] imidoyl chlorides,[13] or allenes.[14] Larock et al. described a more general reaction of pyridines *N*-oxides with benzyne, leading to 3-arylpyridines.[15] Reaction of *N*-oxides with aryl isocyanates is a well-known method of C-2 amination of pyridines.[16]

We have previously developed a cycloaddition reaction between *N*-oxides **1** and perfluoroalkenes (HFP, hexafluoropropene; PFP, 2*H*-pentafluoropropene) as a general method of preparation of 2-fluoroalkylazines (Scheme 1).[17] According to our hypothesis, the initially formed isoxazolidine cycloadduct **2** probably undergoes rearomatization and ring opening to acyl fluoride **4**, which is quenched with an O−H, S−H, or N−H nucleophile to give an ester or an amide of 2-heteroaryl-perfluoropropionic acid **5**. With water as a nucleophile, the resulting carboxylic acid undergoes spontaneous decarboxylation to give an azine with a partially fluorinated alkyl substituent **6**. Both theoretical[18] and experimental[14,16,19] studies indicate that similar 1,3-dipolar cycloadditions involve [1,5]-rearranged products of the type **3**. However, the explanation for the formation of products **5** and **6** does not require the intermediacy of **3**, nor is the formation of **3** possible for 5-membered *N*-oxides which readily undergo the reaction in Scheme 1 as well. The objective of the current work was to determine if simple terminal difluoroalkenes could enter an analogous reaction with *N*-oxides and nucleophiles to give bis(aryl)acetic acids **8** and bis(aryl)methanes **9**[20] in a one-pot, three-component process (Scheme 1).

In recent years, 1,1-difluoroalkenes have become readily available through a variety of synthetic methods.[21] 1,1-Difluorostyrenes used in this study were obtained using a more classical Wittig approach from $CF_2Br_2$ or $ClCF_2CO_2Na$, $PPh_3$, and aromatic aldehydes or ketones (Scheme 2). The latter method proved superior, as it usually gave better yields of **7**, worked for ketones, and avoided the use of $CF_2Br_2$, which is a potent ozone depleting substance.

In the initial experiments, the reactions of 1-benzyl-4,5-dimethylimidazole 3-oxide **1a** with difluorostyrenes **7** and MeOH were attempted at rt in solvents of different polarity (PhMe, DCM, DMF, etc.). Gratifyingly, after 24−48 h the expected compounds **8** were formed as sole products, but in low yields ( < 15%) due to low conversion.

**Scheme 2.** Substrates for the Cycloaddition Reaction




**7a** ($R^1$ = H, Ar = 1-naphthyl)
**7b** ($R^1$ = H, Ar = 4-$BrC_6H_4$)
**7c** ($R^1$ = H, Ar = 2,3-$Cl_2C_6H_3$)
**7d** ($R^1$ = H, Ar = 4-$MeO_2CC_6H_4$)
**7e** ($R^1$ = H, Ar = 3-$O_2NC_6H_4$)
**7f** ($R^1$ = H, Ar = 4-$NCC_6H_4$)
**7g** ($R^1$ = H, Ar = 2-thiophenyl)
**7h** ($R^1$ = H, Ar = *N*-MOM-2-pyrrolyl)
**7i** ($R^1$ = Me, Ar = 3-$O_2NC_6H_4$)

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At 50 °C the reactions of **1a**, **7b**, and MeOH gave the highest yields of **8b** in polar solvents. Oxygen-containing solvents, in particular THF and AcOEt, proved to be the optimal reaction media, giving clean reactions with fairly good yields, which could be further increased by increasing the temperature to 70 °C. In THF **8b** was obtained in 72% yield after 48 h, with 20% of **7b** recovered. Even though 2 equiv of HF are released during the reaction, the addition of amine ($NEt_3$ or pyridine) did not have any positive influence on the yield or reaction time. It also suggests that HF does not have an autocatalytic effect on the reaction. The reaction in MeOH as solvent provided only traces of **8b**, perhaps due to deactivation of *N*-oxide by hydrogen bonding and solvation by MeOH.

Reactions of 5-membered *N*-oxides **1a**–**d** with various difluorostyrenes and alcohols in THF at 70 °C, 48 h (method A) or in DMF, rt, 1–2 weeks (method B) are shown in Table 1.

In the reactions with difluorostyrenes containing both electron-poor and -rich aryl substituents, imidazole *N*-oxide **1a** gave the expected esters **8a**–**i**, in nearly all cases in moderate or good yields. Lower yields were the result of incomplete conversion of substrates, rather than decomposition or formation of any side products. Reactions of electron-rich alkenes were much slower than of alkenes with electron-withdrawing or neutral substituents. Nitro-substituted alkene **7e** gave good yields of **8e** and **8j** even at lower temperature (40 °C). On the other hand, the reaction of the most electron-rich pyrrole difluoroalkene **7h** was very sluggish and the majority of unreacted alkene was recovered. This example demonstrates that even a relatively labile methoxymethyl protecting group is inert under the reaction conditions.

The reaction of alkene **7i** derived from a ketone (3-nitroacetophenone, $R^1$ = Me) was somewhat slower, probably due to steric hindrance caused by the methyl substituent, but it cleanly afforded product **8i** with a quaternary carbon atom.

*N*-Oxide **1c** containing a naphthalene unit condensed with the imidazole ring gave the respective ester **8l** in high yield (91%) which can be explained by a faster cycloaddition step owing to the lower dearomatization energy of **1c** compared to *N*-oxides **1a** or **1b**.

Thiazole *N*-oxide **1d** reacted with alkenes **7b** and **7e** more slowly than imidazole *N*-oxides **1a**–**c**, but it gave analogous esters **8m** and **8n**.

Surprisingly, an alkene with an aliphatic substituent, $C_7H_{15}CH{=}CF_2$, did not undergo any reaction even under relatively forcing conditions (DMF, 100 °C, 7 days).

According to Scheme 1, finishing the reaction with water should result in the formation of the respective carboxylic acid, the decarboxylation of which would lead to 2-benzylimidazole **9**.[22] Indeed, a reaction of *N*-oxide **1a** with alkenes **7a**, **b**, **e**, **i** and of **1c** with **7e** in the mixture THF–water 5:1 gave the corresponding products **9a** (70%), **9b** (65%), **9e** (84%), **9i** (32%), and **9l** (56%). Hydrolysis of **8a** with $LiOH \cdot H_2O$ gave **9a** in 93% yield.

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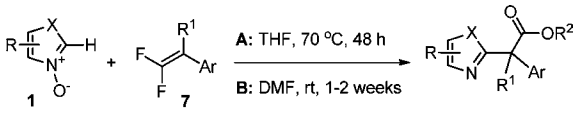
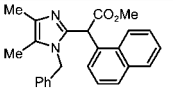
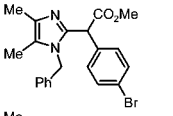
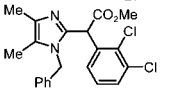
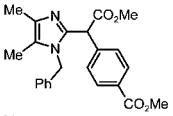
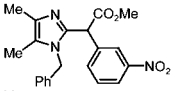
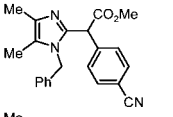
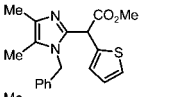
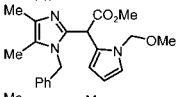
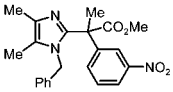
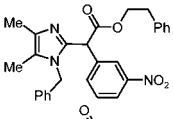
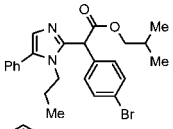
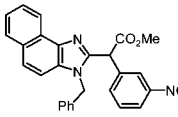
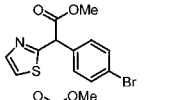
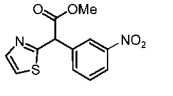
**Table 1.** Reactions of Imidazole and Thiazole *N*-Oxides with Difluorostyrenes and Alcohols

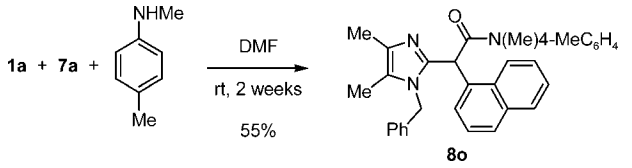



| substrates | product | | method | yield[a] |
|---|---|---|---|---|
| **1a**, **7a**, MeOH |  | **8a** | **A** | 70%[b] |
| | | | **B** | 44%[c] |
| **1a**, **7b**, MeOH |  | **8b** | **A** | 72% |
| | | | **B** | 47%[c] |
| **1a**, **7c**, MeOH |  | **8c** | **A** | 87% |
| | | | **B** | 51%[c] |
| **1a**, **7d**, MeOH |  | **8d** | **A** | 50% |
| **1a**, **7e**, MeOH |  | **8e** | **A** | 65%[d] |
| | | | **B** | 74%[e] |
| **1a**, **7f**, MeOH |  | **8f** | **A** | 92% |
| **1a**, **7g**, MeOH |  | **8g** | **A** | 45% |
| **1a**, **7h**, MeOH |  | **8h** | **A** | 13%[f] |
| **1a**, **7i**, MeOH |  | **8i** | **A** | 26% |
| **1a**, **7e**, $Ph(CH_2)_2OH$ |  | **8j** | **A** | 72%[d] |
| **1b**, **7b**, *i*-BuOH |  | **8k** | **A** | 35% |
| **1c**, **7e**, MeOH |  | **8l** | **A** | 91% |
| **1d**, **7b**, MeOH |  | **8m** | **A** | 22%[g] |
| **1d**, **7e**, MeOH |  | **8n** | **A** | 43%[g] |

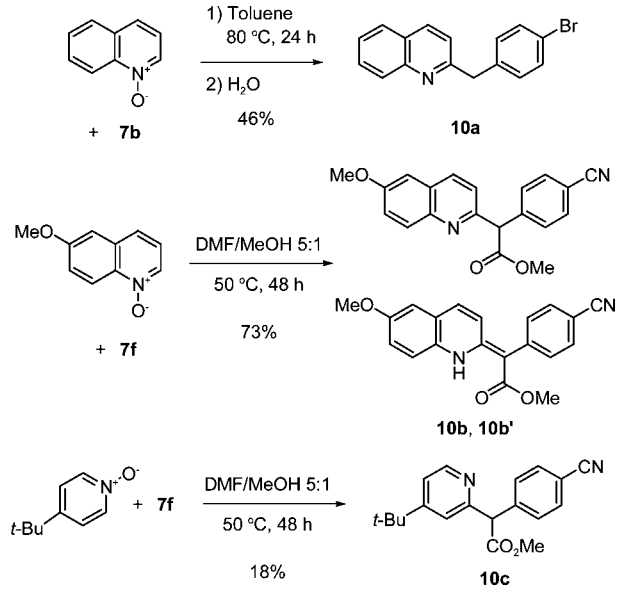
[a] Isolated yields. [b] 72 h. [c] 1 week. [d] 40 °C. [e] 2 weeks. [f] 93% based on recovered **7h**. [g] 50 °C, 4 days.

Reactions of **1** and **7** in a dry solvent, without any nucleophile, after aqueous workup give products **9** as well.

**Scheme 3.** Synthesis of a Tertiary Amide




**Scheme 4.** Reactions of Quinoline and Pyridine *N*-Oxides




It demonstrates that the presence of alcohol is not necessary for the reaction between *N*-oxide and difluorostyrene.

The formation of products **8** and **9** is consistent with the general mechanistic concept shown in Scheme 1. However, further studies will be necessary to elucidate the actual mechanism of the reaction. The structure of compounds **8** and **9** was confirmed by their IR, MS, HRMS, and $^{1}H$ and $^{13}C$ NMR spectra, and in representative cases by COSY, DEPT, and HSQC NMR experiments.

Using a secondary amine *N*-methyl-4-methylaniline instead of an alcohol allowed an amide of aryl(heteroaryl)-acetic acid **8o** to be obtained in 55% yield (Scheme 3). Side products which could be formed in the direct reaction of amine and **7a** were not observed.[23]

Preliminary experiments indicate that 6-membered *N*-oxides are viable substrates as well (Scheme 4), but they are considerably less reactive than **1a**–**d**. The reaction of quinoline *N*-oxide with alkene **7b** in toluene at 80 °C after aqueous workup gives the expected decarboxylated product **10a** in moderate yield. Reactions of 6-methoxyquinoline and 4-*tert*-butylpyridine *N*-oxides with **7d** in DMF–MeOH 5:1 give methyl esters **10b** and **10c**. In a freshly prepared $CDCl_3$ solution the product **10b** exists as a 1:1.5 mixture of tautomers **10b** and **10b′**, the latter probably stabilized by an intramolecular hydrogen bond. In contrast, all compounds **8** ($R^1$ = H) at least in solution exist exclusively in their fully aromatic forms.

In conclusion, a novel synthetic method has been developed which allows benzylic primary, secondary, and tertiary substituents to be introduced into heterocyclic rings in the position adjacent to nitrogen in a completely selective manner. Especially with 5-membered heterocycles the reaction can be achieved under relatively mild and neutral conditions. Further studies directed toward expanding the scope of the reaction on other heterocyclic systems and other types of alkenes, as well as elaboration of its diastereoselective variant, are underway in our laboratory.

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**Supporting Information Available.** Full experimental procedures and characterization data, copies of NMR spectra of compounds **7**–**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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