Cycloaddition

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Stereoselective Synthesis of α-Diazo Oxime Ethers and Their Application in the Synthesis of Highly Substituted Pyrroles through a [3+2] Cycloaddition**

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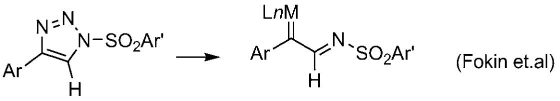
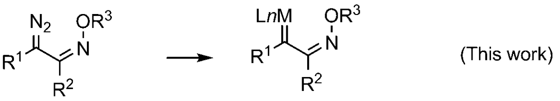
α-Diazocarbonyl compounds have been extensively studied for their synthetic applications over the last few decades.[1] They are well recognized as the precursors for highly reactive metal carbenoids, particularly with copper[2] and rhodium,[3] which promote a number of unique transformations including addition,[4] C–H insertion,[5] and ylide formation.[6] In contrast, their nitrogen analogues, that is, α-diazo imines, remain unexplored largely because of their limited availability as they undergo spontaneous cyclization to produce 1,2,3-triazoles.[7] Recently, Fokin and co-workers reported the use of *N*-sulfonyl 1,2,3-triazoles **1** as a precursor for α-imino carbenoids **2** [Eq. (1)].[8] Murakami et al. also used this ring-chain tautomerization of *N*-sulfonyl triazoles for the synthesis of pyrroles by nickel-carbenoid-mediated alkyne insertion albeit with low regioselectivity.[9] Herein, we wish to report the use of α-diazo oxime ethers **3** as general precursors of α-oximino carbenoids **4** and their application in the synthesis of highly substituted pyrroles [Eq. (2)].



1 **2**

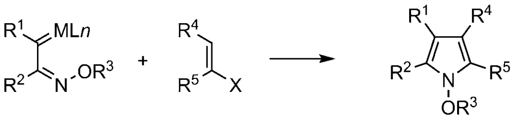
(1)



3 **4**

(2)

Pyrroles, one of the most valuable N-heterocyclic compounds, constitute the core motif of natural products,[10] medicinal agents,[11,12] and conducting polymers.[13] In addition, *N*-alkoxy pyrroles are used as insecticides for crop protection.[14] These properties continue to stimulate interest in the development of new synthetic methods for pyrroles. In general, pyrroles are prepared by cycloaddition reactions[15] ([4+1] and [3+2]) or intramolecular cyclization reactions.[16] In addition, ring contraction of N-heterocycles[17] and three-component reactions[18] have also been employed for the preparation of pyrroles. A few studies using α-diazocarbonyl compounds in the synthesis of pyrroles have also been reported.[19] Despite a number of synthetic methods available for pyrroles, the need for the development of an efficient method that provides highly substituted pyrroles still remains. We envisaged that the reaction of α-oximino carbenoids with alkenes would result in the formation of pyrroles through electrophilic attack of α-oximino carbenoid [Eq. (3)].



(3)

Our efforts to synthesize α-diazo oxime ethers began with a judicious choice of a precursor. Since triazole formation is triggered by a lone pair disposed *cis* to a diazo group, we reasoned that it could be avoided if the geometry of an imine is controlled such that the lone pair is disposed *trans* to the diazo group. It was also anticipated that the reduced basicity of oximes over imines would lead to an increased stability of the corresponding diazo compounds. Thus, when a 1:1 mixture of the *cis/trans* oxime ether **5a** was treated with *p*-toluenesulfonyl azide as a diazo transfer agent, we were delighted to observe that the diazo product **6a** was formed in 51% yield as a single isomer along with triazole **7a** (30%; Scheme 1). The *cis* geometry of the diazo compounds was unambiguously assigned from the single-crystal structure of the analogue **6c** (Figure 1).[20]

Encouraged by this result, we set out to improve the yield by screening several diazo transfer agents and solvents (Table 1). Whereas arylsulfonyl azides having electron-donating groups such as amido and methyl groups resulted in poor yields (Table 1, entries 2 and 3), those with strong electron-withdrawing groups gave improved results. Remarkably, the use of 4-nitrobenzenesulfonyl azide provided the *cis*-diazo product in 64% yield from a 1:1 mixture of the *cis/trans* oxime ether **5a** (Table 1, entry 5). We reason that a rapid equilib-

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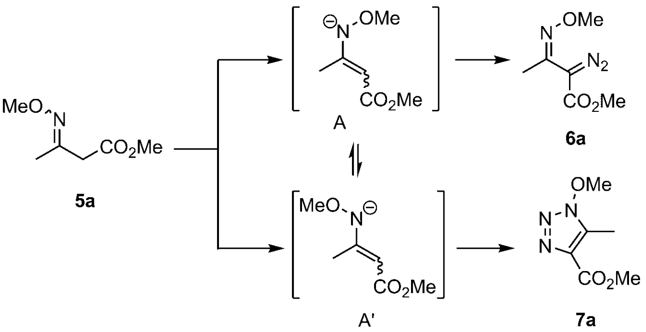
rium between A and A′ allows for the preferential formation of diazo compound **6a** over triazole **7a**, irrespective of the ratio of the oxime isomers (Scheme 1). This was additionally corroborated by the reaction of the *cis*-isomer **5g**, which furnished *cis*-diazo product **6g** in excellent yield (78%) under identical reaction conditions (Table 2, entry 6). The introduc-



Scheme 1. Diazo transfer reaction on the mixture of *cis/trans* oxime isomers **5a**.

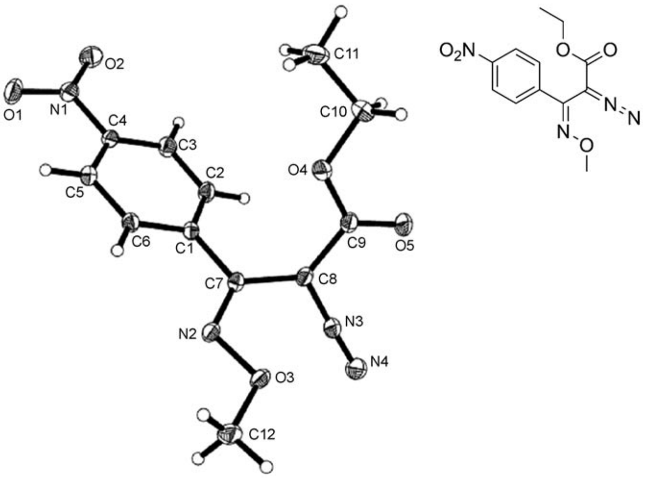
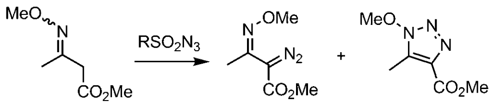


Figure 1. X-ray crystal structure of **6c**. The thermal ellipsoids are drawn at 50% probability.

Table 1: Optimization of diazo transfer reaction.[a]

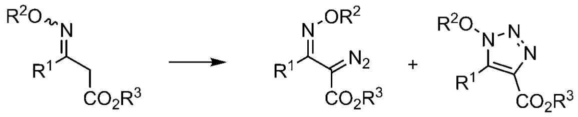


5a (1:1) **6a** **7a**

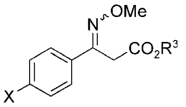
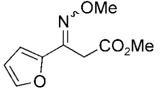
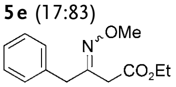
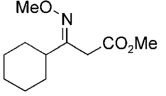
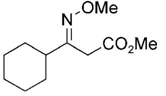
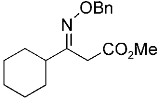
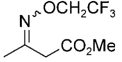
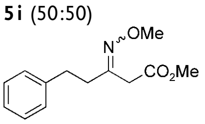
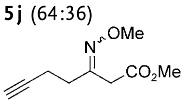
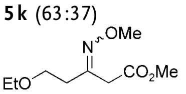
Entry	R	Solvent	Yield [%][b,c]	
			6a	**7a**
1	CH_3	CH_3CN	20	11
2	4-$NHAcC_6H_4$	CH_3CN	41	32
3	4-$CH_3C_6H_4$	CH_3CN	51 (35)[d]	30
4	4-$CF_3C_6H_4$	CH_3CN	56	29
5	4-$NO_2C_6H_4$	CH_3CN	64	33
6	2-$NO_2C_6H_4$	CH_3CN	63	34
7	CF_3	CH_3CN	36	40
8	2,4-$(NO_2)_2C_6H_3$	CH_3CN	63	20
9	4-$NO_2C_6H_4$	EtCN	55	34
10	4-$NO_2C_6H_4$	THF	42	32
11	4-$NO_2C_6H_4$	toluene	30	25
12	4-$NO_2C_6H_4$	CH_2Cl_2	37	33
13	4-$NO_2C_6H_4$	DMF	41	27
14	4-$NO_2C_6H_4$	Et_2O	46[d]	23

[a] Reaction conditions: oxime ether **5a** (1 equiv), $ArSO_2N_3$ (1.1 equiv), DBU (1.1 equiv), solvent (5 mL mmol^{-1}), −20 °C→RT, 3 h. [b] Yields of isolated products. [c] Single isomers were obtained in all cases. [d] Yield at 0 °C. DMF = *N,N'*-dimethylformamide, THF = tetrahydrofuran.

Table 2: Preparation of α-diazo oxime ethers.[a]



5 **6** **7**

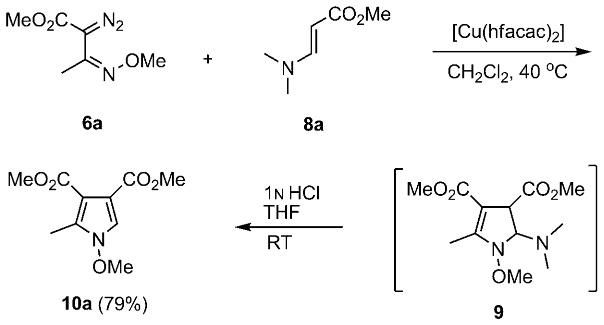
Entry	5[b]	6/7	Yield of 6 [%][c,d]
			
1	**5b** (5:95) X = H, R^3 = Me	30:1	91
2	**5c** (12:88) X = NO_2, R^3 = Et	11:1	85
3	**5d** (0:100) X = OMe, R^3 = Et	22:1	89
			
4	**5e** (17:83)	17:1	85
			
5	**5f** (72:28)	18:1	72
			
6	**5g** (100:0)	16:1	78
			
7	**5g’** (0:100)	21:1	84
			
8	**5h** (0:100)	14:1	85
			
9	**5i** (50:50)	2.8:1	61
			
10	**5j** (64:36)	4.9:1	78
			
11	**5k** (63:37)	3.2:1	74
			
12	**5l** (56:44)	2.8:1	69

[a] Reaction conditions: oxime ether (0.5 mmol), 4-nitrobenzenesulfonyl azide (0.55 mmol), DBU (0.55 mmol), CH_3CN (2.5 mL), −20 °C→RT, 3 h. [b] Shown are the major isomers (isomer ratios in the parentheses). [c] Yields of isolated products. [d] Single isomers were obtained in all cases.

tion of an additional nitro group, that is, 2,4-dinitrobenzenesulfonyl azide, did not improve the yield (Table 1, entry 8). Also, screening of solvents identified acetonitrile as an optimal solvent.

With the optimal reaction conditions in hand, we next examined the substrate scope of the reaction (Table 2). The oxime ethers (**5a–l**) were readily prepared from the corresponding β-ketoesters and methoxyamine in pyridine. The ratios of *cis/trans* isomers were determined by ^{1}H NMR analysis.[21] Consistent with the results in the optimization studies, *cis*-diazo products were obtained as single isomers in good yields. Substrates with aromatic, β-branched primary and secondary alkyl groups gave diazo products in excellent selectivities (Table 2, entries 1–8). Although those substrates with sterically less demanding substituents, such as linear alkyl chains, typically resulted in lower selectivity (Table 2, entries 9–12), the fact that diazo compounds are produced as the major products indicates that both steric and electronic effects are at play. The yields of the diazo compounds were generally higher than those anticipated from the isomer ratios of the corresponding starting materials owing to the rapid equilibrium of the isomers. Thus, it readily allows access to geometrically pure α-diazo oxime ethers from the mixtures of isomers. An examination of the ether moiety of oximes showed that a wide range of substitutions is tolerated including benzyl and trifluoroehtyl groups, thereby adding another site of structural diversity (Table 2, entries 8 and 9).

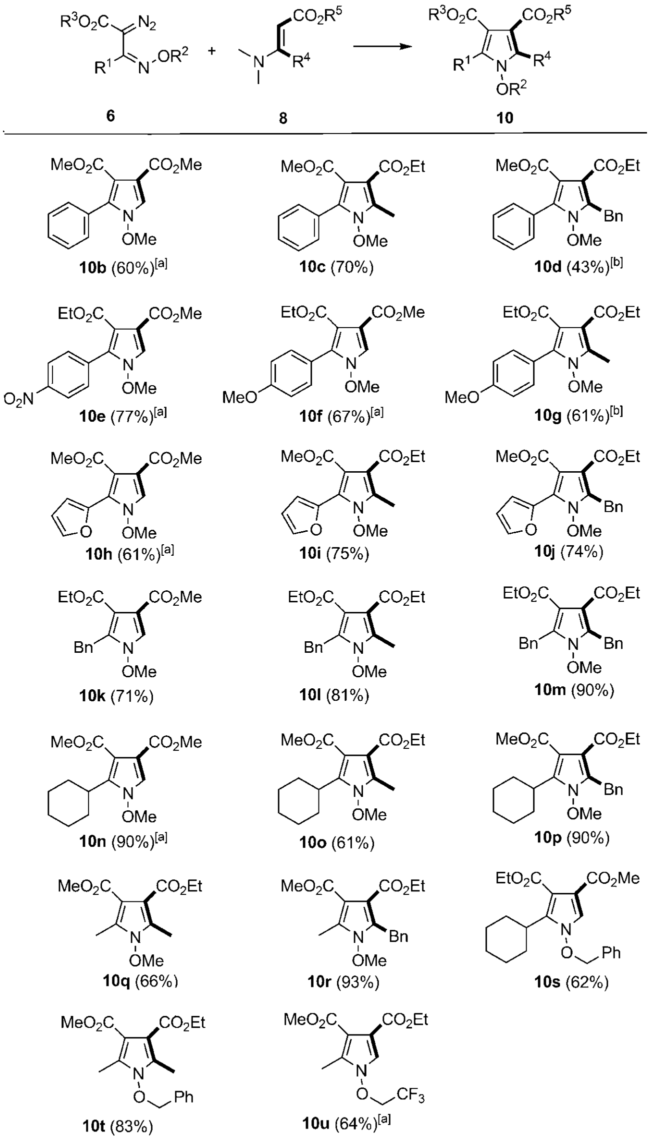
With the various α-diazo oxime ethers in hand, we turned our attention to the synthesis of pyrroles through a [3+2] cycloaddition. We observed that the α-diazo oxime ether **6a** readily reacts with 3-aminoalkenoate **8a** in the presence of a catalytic amount of [Cu(hfacac)$_2$] (hfacac = hexafluoroacetylacetonate) to furnish dihydropyrrole **9** that undergoes loss of dimethylamine under acidic conditions to give *N*-methoxy pyrrole **10a** in 79% yield (Scheme 2).[22]



Scheme 2. Synthesis of pyrrole **10a** through [3+2] cycloaddition of **6a** and **8a**.

Screening of catalysts revealed that Cu(OTf)$_2$ as well as [Cu(hfacac)$_2$] afforded the pyrrole **10a** in comparable yields after treatment with acid (see the Supporting Information). Other catalysts such as [Rh$_2$(OAc)$_4$], [Ni(acac)$_2$], and [Pd(acac)$_2$] (acac = acetylacetonate) that are commonly employed in the decomposition of diazo compounds afforded poor results. Interestingly, [Cu(tfacac)$_2$] (tfacac = trifluoroacetylacetonate) and [Cu(acac)$_2$] gave the product in 42% and 2% yield, respectively. These results indicate that the reaction requires highly electrophilic carbenoids. Although the initial dihydropyrrole cycloadducts **9** partially undergo thermal elimination of dimethylamine resulting in the formation of pyrroles, acid treatment was required to complete the elimination. In most cases, it was promoted simply by treating the reaction mixture with 1N HCl. However, dihydropyrroles substituted with aryl groups at the 2-position were found to give complex mixtures upon treatment with 1N HCl. This was overcome by switching to TFA which led to clean formation of 2-aryl pyrroles.

To examine the substrate scope, we performed the reaction with several structurally diverse α-diazo oxime ethers to afford highly substituted pyrroles in good to

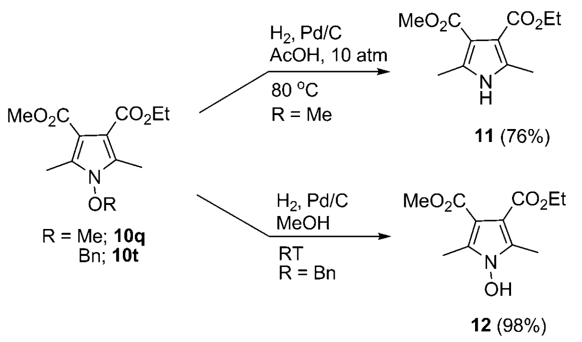


Scheme 3. [3+2] Cycloaddion of α-diazo oxime ethers with 3-aminoalkenoates. Reaction conditions: α-diazo oxime ether (2.0 equiv), 3-aminoalkenoate (1 equiv), Cu(hfacac)$_2$ (4 mol%), dichloroethane, 60 °C, 4 h; 1N HCl, THF, RT, overnight. The reported yields in parentheses are of the isolated product. Yields are reported with respect to 3-aminoalkenoates. [a] TFA (1.2 equiv) in dichloroethane was employed instead of 1N HCl. [b] 60 °C, 16 h. Bn = benzyl.

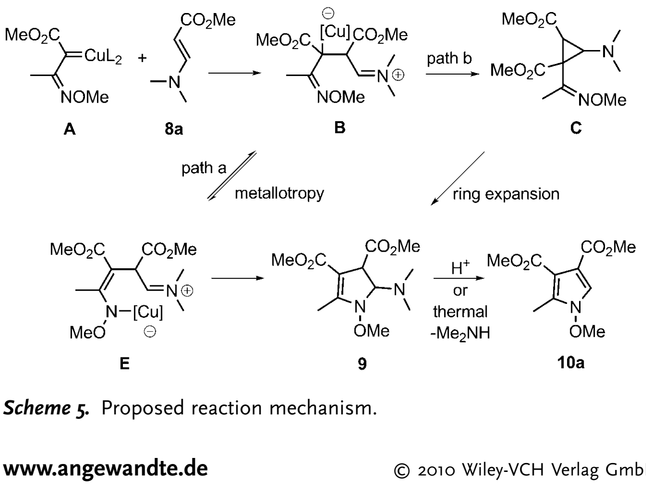
excellent yields (Scheme 3). Sterically demanding substrates were well tolerated to give tetra- and pentasubstituted pyrroles in good yields. 2-Aryl pyrroles (**10b–g**) including 2-furanyl pyrroles (**10h–j**) were successfully prepared by employing the corresponding α-diazo oxime ethers. The electronics of the aromatic groups did not appear to influence the cycloaddition process, as substrates with phenyl groups substituted with methoxy or nitro groups gave comparable product yields (**10e–g**). Substitution on the oxime ether moiety is not limited to methyl group, but those with benzyl and trifluoroethyl groups were equally efficient to give *N*-benzyloxypyrroles **10s** and **10t** and *N*-trifluoroethoxypyrrole **10u** in high yields offering a route to highly substituted pyrroles.

Considering the prevalence of N−H and *N*-hydroxy pyrrole derivatives, we examined the feasibility of accessing these compounds. Thus, subjection of *N*-methoxy pyrrole **10q** to hydrogenolysis conditions (Pd/C, AcOH, 10 atm, 80 °C) smoothly provided the reduction product **11**; elevated pressure was required owing to the steric hindrance (Scheme 4). *N*-hydroxy pyrrole **12** was also readily prepared by hydrogenolysis of the benzyl group.

Mechanistically, we propose that the reaction is initiated with the nucleophilic addition of the enamine to the electrophilic carbenoid **A** resulting in zwitterionic intermediate **B** (Scheme 5). Although it warrants further investigation, two plausible reaction pathways are shown. Path a involves metallotropy of a C- to N-metalated intermediate and subsequent nucleophilic addition to iminium ion **E**.[23] Alternatively, the intermediate **B** undergoes cyclopropanation to **C**, which then undergoes ring expansion (path b).[24] Finally, acid-promoted or thermal elimination of dimethylamine results in the formation of pyrrole.



Scheme 4. Derivatization of *N*-alkoxy pyrroles to N−H pyrrole **11** and *N*-hydroxy pyrrole **12**.



Scheme 5. Proposed reaction mechanism.

In summary, we have described the stereoselective synthesis of α-diazo oxime ethers, a source of α-oximino carbenoids, from the mixture of *cis/trans* β-oximino esters in good to excellent yields. We have also exploited the α-oximino carbenoids for the synthesis of highly substituted *N*-alkoxy pyrroles through [3+2] cycloaddition reactions with enamines.

Experimental Section

General procedure for α-diazo oxime ethers: DBU (1.1 equiv) was added dropwise to a solution of β-oximino ester (1 equiv) and 4-nitrobenzenesulfonyl azide (1.1 equiv) in CH_3CN at −20 °C. The resulting orange-colored solution was stirred for 2 h at −20 °C and then slowly brought to room temperature. The solvent was then removed under reduced pressure and the crude material was purified by flash chromatography.

General procedure for *N*-methoxy pyrrole: A solution of α-diazo oxime ether (2 equiv) and enamine (1 equiv) in dichloroethane was added to anhydrous [Cu(hfacac)$_2$] (4 mol %) at room temperature. The reaction mixture was heated to 60 °C and the temperature was maintained until the diazo compound was fully consumed as determined by TLC. After concentration of the reaction mixture, the crude material dissolved in THF was treated with aqueous 1 N HCl, and stirred at RT overnight. Upon completion of the reaction, the solution was filtered through anhydrous $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (hexanes/EtOAc = 9:1) to give the desired product.

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