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COMMUNICATION

Enabling iron catalyzed Doyle-Kirmse rearrangement reactions with *in situ* generated diazo compounds

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Accepted 00th January 20xxKatharina J. Hock,^a Lucas Mertens,^a Renè Hommelsheim,^a Robin Spitzner,^a and Rene M. Koenigs^{a*}

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Slow addition of sodium nitrite allows the *in situ* preparation of highly explosive diazo compounds and enables their safe and scalable application in iron catalyzed rearrangement reactions of allylic and propargylic sulfides. With catalyst loadings as low as 0.1 mol-% an effective entry into α -mercapto-nitriles, α -mercapto-esters and α -trifluoromethyl-sulfides on gram-scale is achieved.

Diazo acetonitrile was first described in 1898.¹ Yet, this particular diazo compounds found surprisingly little attention, which can be attributed to its extraordinary potential for explosions, as stated in 1956 by Dewar and Champion.² It belongs to the group of acceptor-only substituted diazo compound; a class of diazo compounds that has been intensively studied using ethyl diazo acetate as a model substrate.³

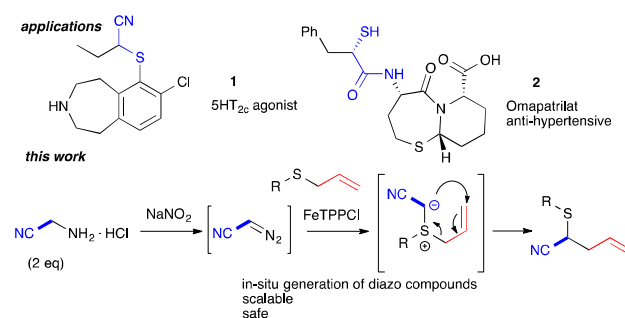
Although diazo acetonitrile offers an elegant entry into nitrile-substituted building blocks for drug discovery,³⁻⁵ it still remains a curiosity in organic synthesis today and only a limited number of reports claim applications in organic synthesis using the preformed reagent as stock solution in organic solvent.³ There is only a single report by Mykhailiuk describing the *in situ* generation of this valuable diazo compound in a one-pot synthesis of pyrazoles, though still limited in scale and applicability.⁵

One concept for safe and scalable reactions with this class of diazo compounds encumbers the accumulation of these hazardous reagents using a slow-release protocol in a biphasic aqueous/organic reaction mixture and sodium nitrite as diazotization reagent.^{5,6} An alternative complementary approach, harnesses continuous-flow protocols for an easily scalable and safe entry into this class of reactive diazo compounds and thus avoiding large amounts of unreacted diazo compounds.^{7,8}

Against the background of our interest in small and reactive diazo compounds and ylide chemistry,^{8,9} we became interested in studying [2,3]-sigmatropic rearrangement

reactions of *in situ* generated diazo acetonitrile. This approach would enable a facile, and safe entry into the ylide chemistry of this diazo compound. In particular, applications of hitherto little explored diazo acetonitrile are highly desired to accentuate its potential as a safe and routinely applicable diazo compound for organic synthesis. The reaction products of this transformation are α -mercapto-nitriles, that are used as 5HT_{2c} agonists (scheme 1, compound **1**)¹⁰ or as anti-hypertensive drugs like Omapatrilat **2**.^{10b} Catalytic sigmatropic rearrangement reactions of ylides generated from diazo compounds and nucleophiles are a powerful tool for the construction of new C-C bonds.¹¹ In particular, the Doyle-Kirmse reaction provides an efficient access to homoallylic systems upon rearrangement.¹²⁻¹⁴ First discovered in the 1960s,¹³ a range of studies reported on applications using different metal complexes in this transformation. They are typically conducted in dry organic solvents, due to the high sensitivity of the intermediate ylide to decomposition reactions. On-water sigmatropic rearrangements have been reported recently, though limited with respect to preformed diazo compounds.^{13a,b,d} Plietker et al. described the only one-pot Doyle-Kirmse protocol, which relies in a first step on the generation of ethyl diazoacetate and subsequent addition of catalyst and substrate furnishes the desired rearrangement product, though only with reduced yield.^{14a}

Scheme 1. Applications of diazo acetonitrile in sigmatropic rearrangement reactions



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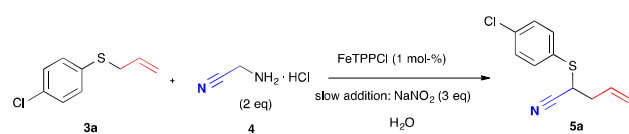
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To the best of our knowledge, the transient *in situ* generation of diazo compounds on-water followed directly by carbene formation and sigmatropic rearrangement has not been reported to date.

Encouraged by the recent reports on biphasic and on-water reactions of diazo compounds, we started our investigations by examining the sigmatropic rearrangement of allyl sulfide **3a** and amino acetonitrile hydrochloride (**4**) using water as solvent. Slow addition of an aqueous solution of sodium nitrite results in the *in situ* generation of diazo acetonitrile, which forms a metal carbene or carbenoid species that undergoes ylide formation with **3a** followed by sigmatropic rearrangement and formation of the homoallylic nitrile **5a**. To our delight Rh₂OAc₄ and Co(salen) provided an entry to α -mercapto-nitriles in acceptable yield (table 1, entry 1 and 2). Manganese complexes or other iron or cobalt salts did not provide the desired product.¹⁵ Noteworthy, changing to FeTPPCI furnished the desired homoallylic nitrile **5a** with excellent yield using only 1 mol-% of catalyst loading.¹⁶ Concentration had a significant effect on the reaction yield and 0.4 M solution in the presence of small amounts of dichloromethane provided the desired rearrangement product **5a** in almost quantitative yield. Interestingly, the more reactive Fe-F₂₀TPPCI catalyst proved to be inferior compared to the archetypal FeTPPCI catalyst.¹⁶ It should be noted that the catalyst loading can be lowered to 0.1 mol-% without significant loss in product yield (table 1).

Table 1. Survey of different catalysts, additives and reaction conditions.



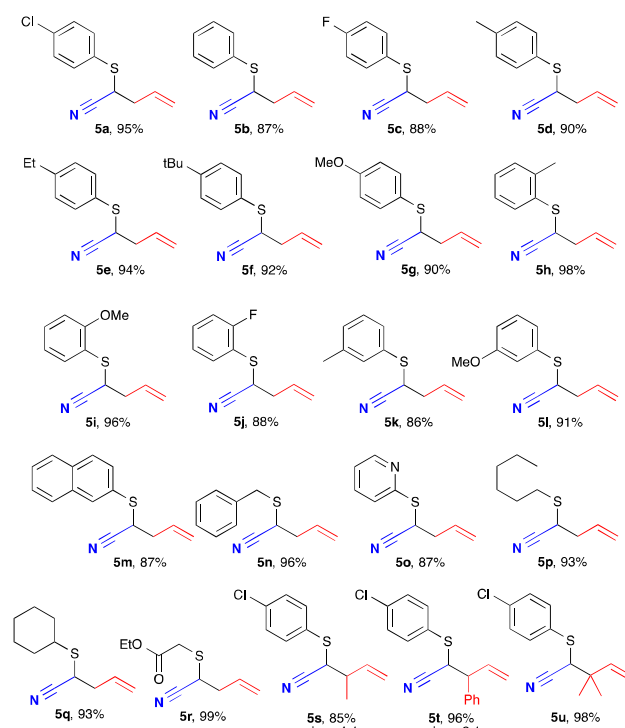
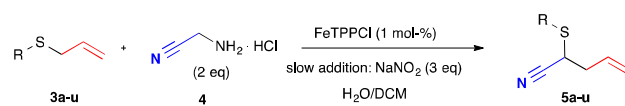
entry ^a	catalyst	mol-%	concentration	yield
1	Co(salen)	1	0.05 M	41
2	Rh ₂ OAc ₄	1	0.05 M	47
3	Mn(salen)	1	0.05 M	no reaction
4	FeTPPCI	1	0.05 M	92
5	FeTPPCI	1	0.1 M	87
6	FeTPPCI	1	0.2 M	81
7	FeTPPCI	1	0.4 M	72
8 ^b	FeTPPCI	1	0.4 M	95
9 ^b	FeTPPCI	0.1	0.4 M	86
10 ^b	Fe(F ₂₀ TPP)Cl	1	0.4 M	82

^aReaction conditions: 0.2 mmol **3a**, 0.1-1 mol-% FeTPPCI, 2 eq **4** were suspended in H₂O. NaNO₂ (3 eq) dissolved in 1 mL water was added 10 h at rt; the resulting mixture was stirred for 5 h at rt; isolated yields. ^b50 μ L DCM were added to the reaction mixture.

With the optimal conditions in hand, we next investigated the substrate scope of the rearrangement reaction of allylic sulfides and *in situ* generated diazo acetonitrile (table 2). Different substituents at the aromatic ring are well tolerated, ranging from halogen, alkyl chains and electron-donating groups. Noteworthy, only little effect of the substitution

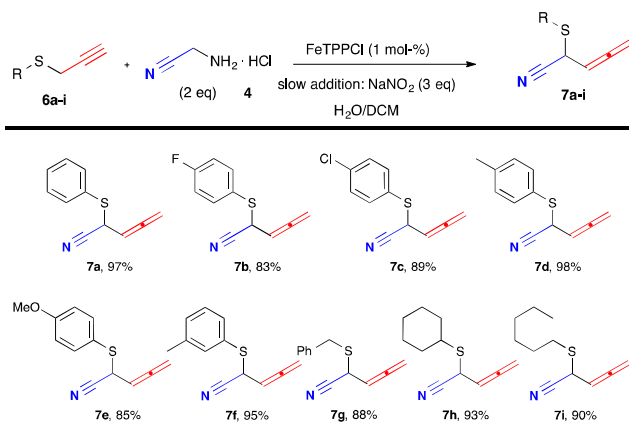
pattern of the aromatic ring was observed. Similarly, carbocyclic-, heterocyclic- and aliphatic substituted allylic sulfides smoothly reacted to the desired rearrangement product. It should be noted that also linear and branched aliphatic, benzyl- or ester- substituted allyl sulfides gave the homoallylic nitriles with excellent yield (table 2). For example, ethyl glycolate derivative **5r** was obtained with excellent yield (99%). In further studies, we focused on the substitution pattern of the allyl group. Cinnamyl-, crotyl and dimethylallyl-substituted sulfides readily provided the desired rearrangement product, though only little diastereoselectivity was observed (table 2, entry **5s** and **5t**).

Table 2. Substrate scope of allylic sulfides.



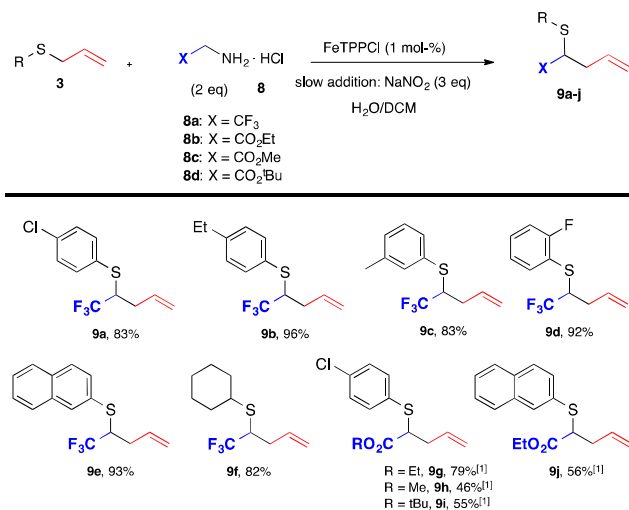
Reaction conditions: 0.2 mmol **3a-u**, 1 mol-% of FeTPPCI, 2 eq **4** were suspended in H₂O (0.5 mL) and DCM (50 μ L). NaNO₂ (3 eq) in 1 mL water was added over 10 h at rt; and then stirred for 5 h; isolated yields.

The rearrangement reaction of propargyl sulfides with diazo compounds yields an allene as the reaction product, that is a versatile functional group for further functionalization. We thus extended our studies towards propargyl sulfides and were delighted to observe that the desired product **7a** could be isolated with an excellent yield (97%). Consequently, we investigated the influence of different substitution patterns at the aromatic ring and different linear and branched aliphatic substituent and the corresponding allenes were isolated in very good to excellent yield (table 3).

Table 3. Substrate scope of propargylic sulfides.

Reaction conditions: 0.2 mmol **6a-i**, 1 mol-% of FeTPPCL, 2 eq **4** were suspended in H₂O (0.5 mL) and DCM (50 μ L). NaNO₂ (3 eq) in 1 mL water was added over 10 h at rt; and then stirred for 5 h; isolated yields.

To further demonstrate the applicability of this protocol, we next investigated the scope of *in situ* generated diazo compounds using different amine hydrochloride salts as diazo compound precursor. In particular, Doyle-Kirmse reaction of allylic sulfides with trifluoro diazoethane results in a concise entry to valuable α -trifluoromethyl sulfides, which are an important class of compounds in pharmaceutical and agrochemical research, for example as stromolysin 1 inhibitors.¹⁷

Table 4. Substrate scope using *in situ* generated trifluoro diazoethane.

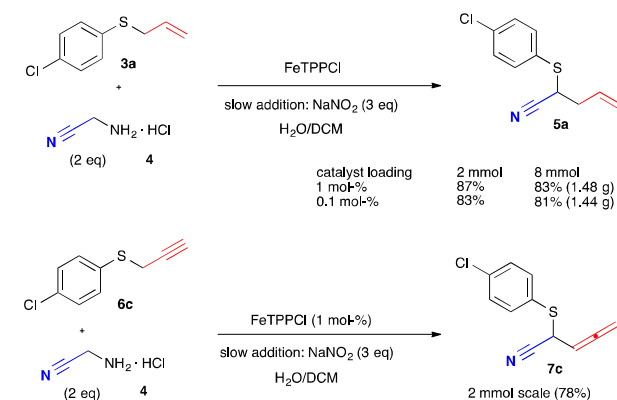
Reaction conditions: 0.2 mmol **3**, 1 mol-% of FeTPPCL, 2 eq **8** were suspended in H₂O (0.5 mL) and DCM (50 μ L). NaNO₂ (3 eq) in 1 mL water was added over 10 h at rt; and then stirred for 5 h; isolated yields. [1] using 2 mol-% of FeTPPCL.

For this purpose we examined trifluoro ethylamine hydrochloride (**8a**), 1 mol-% FeTPPCL as catalyst and slow addition of sodium nitrite and different allylic sulfides (**3**) as substrate for the sigmatropic rearrangement reaction. To our delight, different aromatic and aliphatic allylic sulfides could be

converted to the desired α -trifluoromethyl-sulfides in excellent yield (table 4, entry **9a** to **9f**).

Subsequently, we probed the *in situ* generation of diazo esters and applications in subsequent rearrangement reactions. However, under the present reaction conditions the corresponding α -mercapto-esters were isolated only with moderate to good yield. While *in situ* generated ethyl diazoacetate gave the desired product **9g** and in good yields, the methyl and *tert*-butyl ester were isolated only in moderate yield (table 4, entry **9h** and **9i**).

As described by Curtius in his seminal publication on diazo acetonitrile, safety hazards pose one of the major hurdles while working with this particular reagent. For this reason, the scale-up and thus applicability of reactions employing this particular diazo compound is of great interest. We therefore conducted experiments on large scale and repeatedly increased the reaction scale using both 1 and 0.1 mol-% of catalyst. In initial experiments we performed the reaction on 2 mmol scale, yielding the desired homoallylic sulfide with very good yield. In a further scale-up experiment, we probed an 8 mmol scale and were delighted to observe that **5a** could be obtained with very good yield on gram-scale and only 0.1 mol-% of FeTPPCL as catalyst. Similarly, propargyl sulfide **6c** could be smoothly converted on 2 mmol scale to the allene **7c**.

Scheme 2. Scale-up and derivatization of the reaction product.

In summary, we have reported a protocol enabling applications of diazo acetonitrile in a safe and scalable fashion. Slow addition of sodium nitrite is key for the transient generation of this highly explosive diazo compound. Subsequent iron catalyzed carbene formation, followed by reaction with allylic and propargylic sulfides, generates an ylide that undergoes sigmatropic rearrangement to furnish valuable α -mercapto-nitriles with catalyst loadings as low as 0.1 mol-% with very good to excellent yield on gram-scale, paving the way for safe and scalable applications of diazo acetonitrile, a reagent that is vastly underestimated from an organic synthesis perspective.

Notes and references

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