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Towards nitrile-substituted cyclopropanes – a slow-release protocol for safe and scalable applications of diazo acetonitrile

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Diazo acetonitrile has long been neglected despite its high value in organic synthesis due to a high risk of explosions. Herein, we report our efforts towards the transient and safe generation of this diazo compound, its applications in iron catalyzed cyclopropanation and cyclopropenation reaction and the gram-scale synthesis of cyclopropyl-nitriles.

The chemistry of diazo compounds has made remarkable advances in the past years. However, the synthetic utility of small, reactive diazo compounds has long been neglected, although they possess great potential for the highly efficient and concise construction of small functional molecules.[1,2]

In particular, diazo acetonitrile represents a very close analogue of ethyl diazo acetate and is almost completely unexplored from a synthetic perspective,[3-7] although it was first described by Curtius in 1898.[3] Over the past decades there is only few reports on diazo acetonitrile, which can be attributed to the high risk of explosions when handling diazo acetonitrile. Phillips and Champion reported serious explosions, while handling this particular diazo compound.[4a]

In the context of our ongoing interest in small and reactive diazo compounds,[8] we decided to investigate diazo acetonitrile in cyclopropanation reactions. The corresponding cyclopropanes represent an important structural class with very interesting biological activity and are currently used as Cathepsin C inhibitors (**1**)[9] or as positive allosteric NMDA receptor modulators (**2**).[10] Interestingly, one of the most simple cyclopropyl nitriles, namely 1-carbonitrile-2-phenyl-cyclopropane (**3a**), is used as a fragrance.[11]

Moreover, the nitrile can be readily reduced to provide methylamino-substituted cyclopropanes, which are highly demanded in drug discovery. For example, Tasimelteon (**4**) contains a central methylamino substituted cyclopropane.[12] This structural motif can be readily obtained from the corresponding nitrile-substituted cyclopropane. Similarly, Levomilnacipran (**5**)[13] and $5HT_{2C}$ agonist **6**[14] contain a prominent *trans*- methylamino cyclopropane.

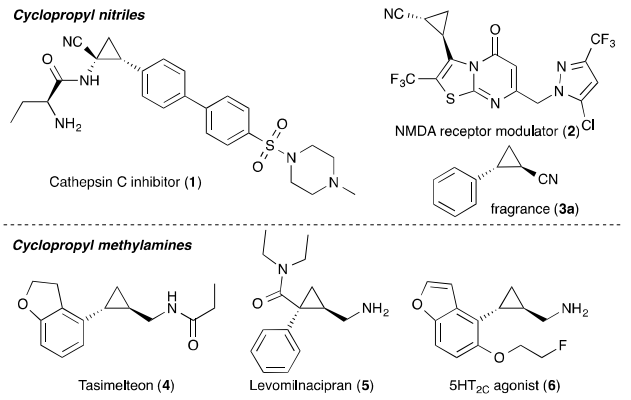

Figure 1. Nitrile- and methylamino- cyclopropanes.

Although many applications of cyclopropyl nitriles in pharmaceutical research are known, current state-of-the-art synthesis protocols require tedious multi-step synthesis, which is far from being atom-economical. Alternatively, metal-mediated atom transfer radical additions[15] or Corey-Chaykovsky cyclopropanation reactions are reported, though poor diastereomeric excess was obtained.[11] There is only a single report in the literature investigating diazo acetonitrile as a preformed reagent, though it suffers from reaction safety, low yields and diastereoselectivity.[5d] To the best of our knowledge, no direct and thus atom-efficient, safe one-step synthesis of cyclopropyl nitriles starting from simple and readily available olefins and bench-stable amines has been reported to date.

Recently, the in-situ generation of diazo compounds from amines and organic[2g,8,16] or inorganic nitrite[6,17] sources attracted the interest of many groups. In particular, phase-transfer protocols proved as a valuable method to prepare different acceptor-only substituted diazo compounds. In 2015, Mykhailiuk reported a first paper on the in-situ generation of diazo acetonitrile in a one-pot dipolar cycloaddition reaction.[6]

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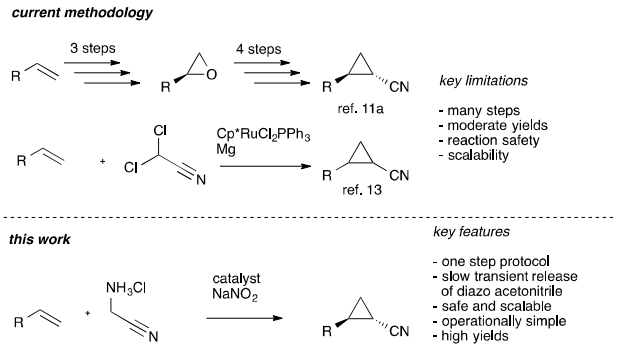
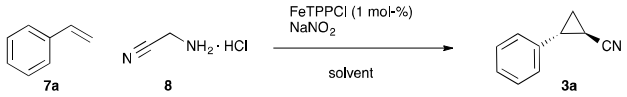


Scheme 1. Catalytic synthesis of cyclopropane nitriles.

Thus, we started our investigations by examining the on water generation of diazo acetonitrile and a subsequent cyclopropanation reaction with styrene. We hypothesized that slow addition of sodium nitrite will result in a slow and continuous release of diazo acetonitrile in the reaction mixture. This slow-release protocol would allow the transient formation of highly reactive and explosive diazo acetonitrile and thus minimize risks while working with this hazardous reagent, when comparing to one-pot batch reactions.[6] Under those conditions, we probed different metal catalysts (e.g. Ru(TPP)CO, Co(salen), Rh_2OAc_4) and were delighted to observe the desired cyclopropane in acceptable yield, although no significant diastereoselectivity was achieved.[18, 19]

Table 1. Survey of different additives and reaction conditions.



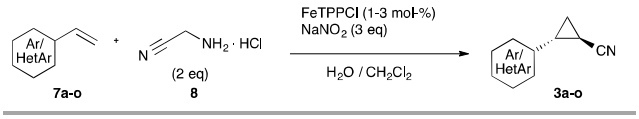
entry	solvent	additive	d.r.	yield
1	water		6:1	70
2	water	DMAP (0.1 eq)	6:1	56
3	water	N-Me imidazole (0.1 eq)	4:1	35
4[b]	water		6:1	42
5	$CHCl_3$: H_2O (30:1)		6:1	40
6	water	PhMe (100µL)	6:1	61
7	water	$CHCl_3$ (100 µL)	6:1	65
8	water	DCM (100 µL)	6:1	81
9[c]	water	DCM (100 µL)	6:1	83

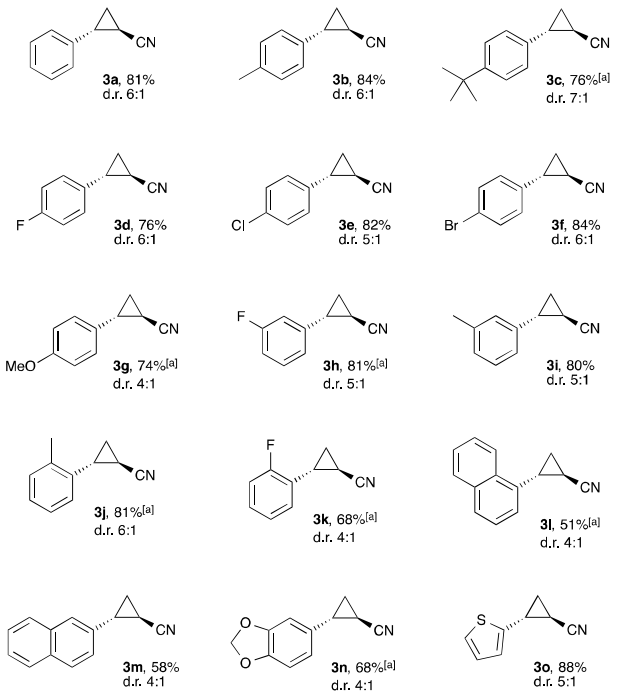
reaction conditions: 0.4 mmol styrene, 1-3 mol-% of FeTPPCl, 2 eq aminoacetontrile hydrochloride were dissolved in 1 mL of solvent indicated. $NaNO_2$ (3 eq) dissolved in 1 mL water was added over a period of 10 h at rt; the resulting mixture was stirred for another 4 h at rt; yields refer to the *trans* product after column chromatography; the d.r. was determined from the crude reaction mixture by ^{1}H-NMR; [b] at 0°C; [c] 3 mol-% FeTPPCl.

If FeTPPCl (table 1) is used as catalyst, a good diastereoselectivity of 6:1 (*trans*:*cis*) was observed and the desired cyclopropane could be isolated in good yield. Different additives such as DMAP or N-methyl imidazole were tested, though no increase in diastereoselectivity or yield was observed. Similarly, lower reaction temperatures did not provide satisfying results (table 1, entry 4). To improve the yield, we next tested phase transfer protocols: large amounts of organic solvent proved to be inferior in terms of product yield (table 1, entry 5). Interestingly, upon addition of a small amount of dichloromethane to the reaction mixture, and thus in a phase transfer protocol with a highly concentrated organic layer, the reaction product was formed in very good isolated yield (table 1, entry 8 and 9).

With the optimal reaction conditions in hand, we then investigated the substrate scope using different styrene derivatives. Different electron-donating and electron-withdrawing substituents and substitution patterns at the aromatic ring were investigated and the corresponding cyclopropanes could be isolated in very good yield with good diastereoselectivity using 1 or 3 mol-% FeTPPCl as catalyst. Similarly, vinyl-substituted naphthalenes (table 2, entry **3l** and **3m**) provided the desired cyclopropanation product in good yield and diastereoselectivity. Further investigations concentrated on sulfur-containing heterocycles, which reacted smoothly to the nitrile-substituted cyclopropane product. It should be noted, that 4-vinyl pyridine did not provide the desired reaction product.

Table 2. Survey of different additives and reaction conditions.





reaction conditions: 0.4 mmol styrene (**7a-o**), 1-3 mol-% FeTPPCl, 2 eq aminoacetonitrile hydrochloride (**8**) were dissolved in H_2O/CH_2Cl_2 (1 mL / 100 µL). $NaNO_2$ (3 eq) dissolved in 1 mL water was added over a period of 10 h at rt; the resulting mixture was stirred for another 4 h at rt; reported yields refer to the *trans* product after column chromatography; the d.r. was determined from the crude reaction mixture by ^{1}H-NMR; [a] using 3 mol-% of catalyst.

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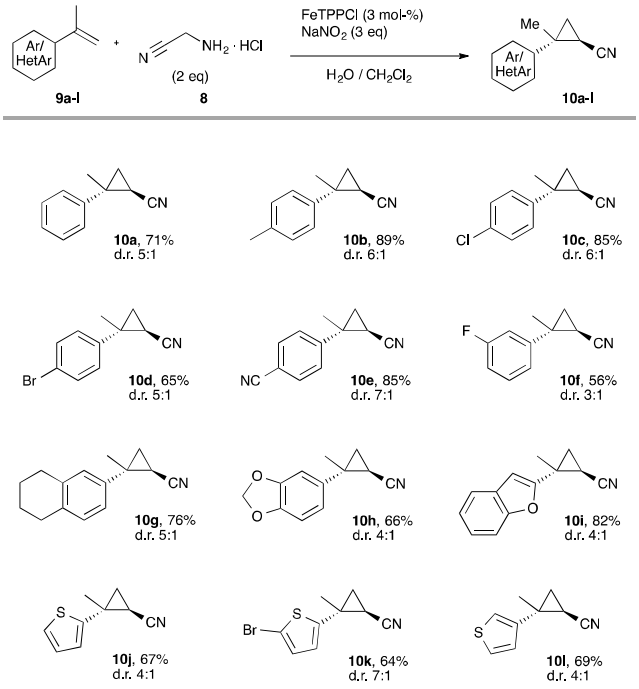
In further studies we probed a range of different α-methyl styrenes, which were readily converted to the corresponding cyclopropyl nitriles with good diastereoselectivity and high yield. Both electron-donating and electron-withdrawing substituents were well tolerated. Similarly, the effect of the substitution pattern of the aromatic ring was investigated, though only a minor influence was observed. Interestingly, different carbocycles as well as oxygen and sulfur-containing heterocycles reacted efficiently to yield the hetero- and carbocyclic cyclopropanes (**10g-l**).

Table 3. Substrate scope of different α-methyl styrenes.

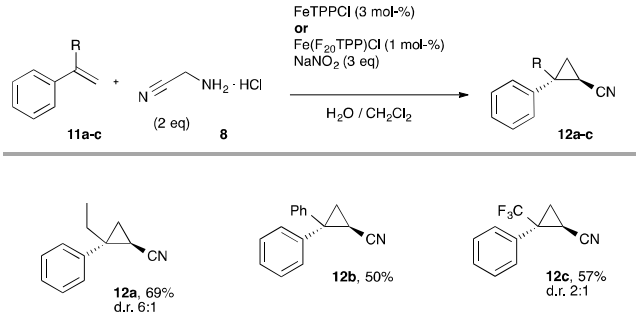


reaction conditions: 0.4 mmol styrene (**9a-l**), 3 mol-% FeTPPCl, 2 eq aminoacetonitrile hydrochloride were dissolved in H_2O/CH_2Cl_2 (1 mL / 100 µL). $NaNO_2$ (3 eq) dissolved in 1 mL water was added over a period of 10 h at rt; the resulting mixture was stirred for another 4 h at rt; reported yields refer to the *trans* product after column chromatography; the d.r. was determined from the crude reaction mixture by ^{1}H-NMR.

Further investigations concentrated on different α-substituted styrenes using iron catalysts. α-ethyl styrene, diphenyl ethylene readily provided the desired cyclopropanation product in moderate to good yield.

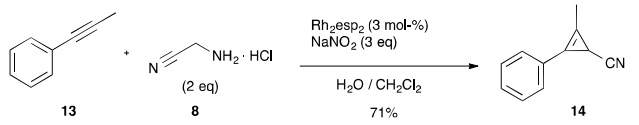
We then hypothesized that electron-poor and thus weakly nucleophilic α-trifluoromethyl styrene derivatives are highly interesting substrates for the construction of trifluoromethyl- and nitrile disubstituted cyclopropanes. To date, there is only one report claiming α-trifluoromethyl styrene in a cyclopropanation reaction using a dimeric Fe(salen) complex as catalyst.[20] Against this background, we became interested in examining our protocol in this particular transformation. Notably, FeTPPCl was almost inactive in the cyclopropanation reaction provding the desired reaction product **12c** only in unsatisfactory yield and diastereoselectivity (yield by ^{19}F-NMR <10%, d.r. 1:1). However, if the more reactive Fe(F_{20}TPP)Cl[19] catalyst was used, α-trifluoromethyl styrene was readily converted to the corresponding trifluoromethyl-substituted cyclopropane **12c** with good yield and little diastereoselectivity. It should be noted that under the present reaction conditions, *trans*-β-methyl styrene, indene or allylbenzene were investigated, though no reaction product was obtained.

Table 4. Substrate scope of different α-methyl styrenes.



reaction conditions: 0.4 mmol styrene (**11a-c**), 3 mol-% FeTPPCl, 2 eq aminoacetonitrile hydrochloride were dissolved in H_2O/CH_2Cl_2 (1 mL / 100 µL). $NaNO_2$ (3 eq) dissolved in 1 mL water was added over a period of 10 h at rt; the resulting mixture was stirred for another 4 h at rt; reported yields refer to the *trans* product after column chromatography; the d.r. was determined from the crude reaction mixture by ^{1}H-NMR.

Furthermore, we investigated cyclopropenation reactions using phenyl-propyne (**13**) and Rh_2esp_2 as catalyst.[19] To our delight, we were able to isolate the desired cyclopropene **14** in good yield (scheme 2). Notably, FeTPPCl did not provide the desired cyclopropene.



Scheme 2. Cyclopropenation reaction with Rh_2esp_2.

The scale-up of transformations using diazo compounds is of particular interest for potential applications involving this class of highly reactive reagents. In particular, diazo acetonitrile has been demonstrated to possess a high risk of explosions and the safe and routine application of this reagent is of primary importance for its use. We therefore decided to evaluate the scalability of this slow-release protocol and were delighted to observe that the gram-scale synthesis of fragrance **3a** proceeded smoothly using 1 mol-% of catalyst and 86% isolated yield. If the more reactive Fe(F_{20}TPP)Cl catalyst was used in this transformation, the catalyst loading can be reduced to as low as 0.03 % and the desired cyclopropyl nitrile **3a** was isolated in good yield.

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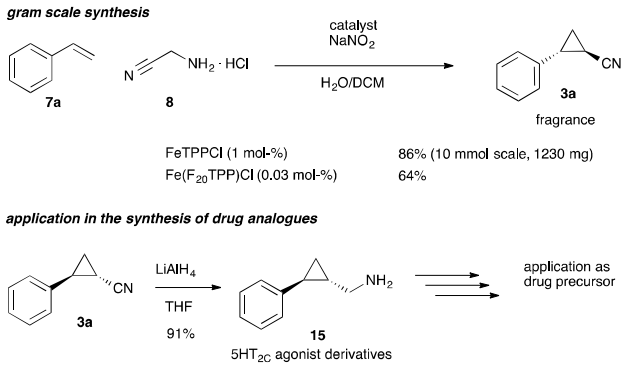

Scheme 3. Gram-scale synthesis and derivatization of the nitrile cyclopropane.

Reduction of the cyclopropyl-nitrile provides a simple and high-yielding access to *trans*-configured cyclopropyl methylamines (**15**) that are key building blocks in drug discovery and used as $5HT_{2c}$ agonists.

In summary, we have established a protocol that allows for the a diastereoselective, catalytic one-step synthesis of high-valued nitrile-substituted cyclopropanes and cyclopropenes. This slow-release protocol enables safe and scalable applications of highly explosive diazo acetonitrile and opens up new synthetic opportunities using this reagent. We were able to demonstrate its synthetic potential on a gram-scale synthesis of vital building blocks for drug discovery.

Notes and references

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18 for details see supporting information.

19 TPP = 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine, F_{20}TPP = 5,10,15,20-Tetrakis(pentafluorophenyl)-21*H*,23*H*-porphyrin, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

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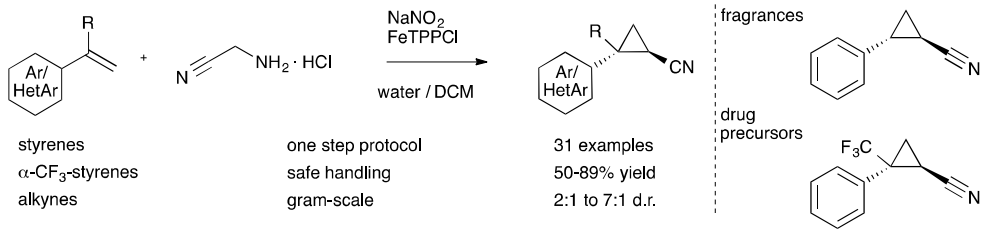

Applications of diazo acetonitrile in cyclopropa(e)nation reactions are realized in a slow-release protocol with bench-stable reagents. The cyclopropyl nitriles are obtained in one-step in good diastereoselectivity on gram-scale providing an efficient entry into this class of fragrances and drug-like molecules.