RCM-Mediated Synthesis of Fluorinated Cyclic Hydrazines

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Abstract: A series of fluorinated cyclic hydrazine derivatives has been prepared in a straightforward manner using ring-closing metathesis (RCM) of fluorinated- and trifluoromethylated olefins as the key step.

Key words: cyclic hydrazines, ring-closing metathesis, fluorinated heterocycles, trifluoromethylated heterocycles

Cyclic hydrazine moieties occur in a wide variety of biologically active compounds. Some examples are shown in Figure 1, such as LY186826 (**1**), which is part of a new class of antibiotics,[1] and piperazic acid (**2**), which is a key component of the class of biologically active sanglifehrins.[2] A recent example comprises hydrazine **3**, which was shown to possess promising activity against type 2 diabetes.[3]

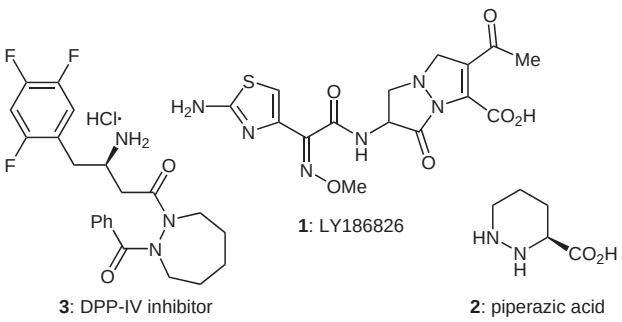
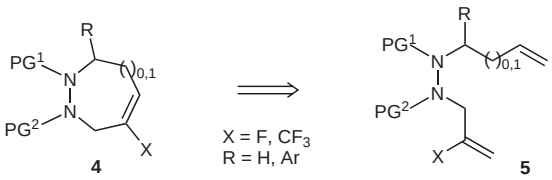


Figure 1 Biologically active cyclic hydrazines

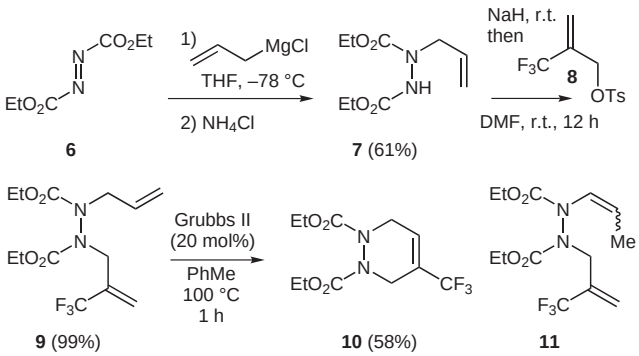
In addition to the existing methods to synthesize cyclic hydrazine derivatives,[4] it was recently demonstrated that ring-closing metathesis (RCM) can also be applied for this purpose.[5] Although these approaches give rise to a large choice of hydrazines of different ring sizes and various substitution patterns, none of them involves the synthesis of fluoride-containing rings. Considering that the introduction of fluoride or fluoride-containing substituents often favorably contributes to the pharmacokinetic profile of bioactive compounds, an awareness that has led to a tremendous increase of new organofluorine compounds and their application in pharmaceutical research,[6] we became interested in the synthesis of fluorinated cyclic hydrazine derivatives. Based on previous experience in our group with preparing cyclic hydrazines,[7] and in conjunction with recent results from our[8] and other groups[9] concerning the RCM-mediated synthesis of N-heterocyclic building blocks, in particular fluorinated[10] and trifluoromethylated heterocycles,[11] we set out to apply RCM as a potential tool to synthesize the corresponding cyclic hydrazines. Although few RCM examples of fluorinated olefins exist,[12] it has never been applied for the synthesis of this particular class of hydrazines that may have potentially unique properties.

Retrosynthetically, readily available fluorinated or trifluoromethylated olefins of type **5** might serve as suitable precursors for the preparation of the target cyclic hydrazines **4** using RCM (Scheme 1).



Scheme 1 Retrosynthetic approach

To initially probe the viability of this strategy, we first aimed at preparing a simple six-membered cyclic trifluoromethylated hydrazine bearing the same protective group on both nitrogens. The required RCM precursor **9** was synthesized through two alkylation steps, starting from diethyl azodicarboxylate **6** (Scheme 2).



Scheme 2 Synthesis of the trifluoromethylated cyclic hydrazine **10**

The first alkylation of azodicarboxylate **6** with allylmagnesium chloride (THF, –78 °C, workup with NH_4Cl) provided the monoalkylated hydrazo ester **7** in 61% yield.[7b]

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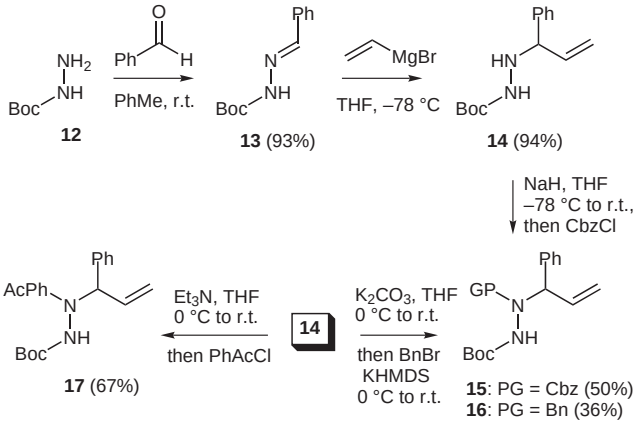
Subsequently, a second alkylation with the allylating reagent **8**[11] provided the RCM precursor **9** in excellent yield. This precursor molecule was then subjected to RCM using the second-generation Grubbs catalyst (Grubbs II, 20 mol%) added in portions over one hour to the reaction mixture in toluene at 100 °C. As anticipated, the cyclization proceeded smoothly to produce the desired cyclic hydrazine **10** in 58%, along with a minor amount (<10%) of the isomerized enamine **11** as the sole byproduct.[13] Although this first example proved the viability of the RCM strategy, it also made clear that isomerization could be a problem. To avoid the side reaction and to be able to introduce additional substituents a somewhat different route was developed for the synthesis of RCM precursors (Scheme 3).

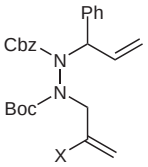
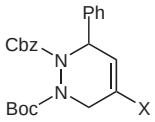
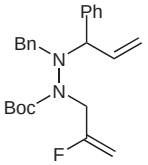
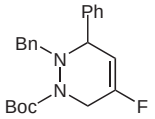
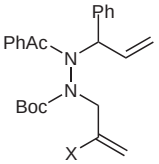
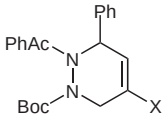


Scheme 3 Synthesis of differentially protected hydrazines **15**–**17**

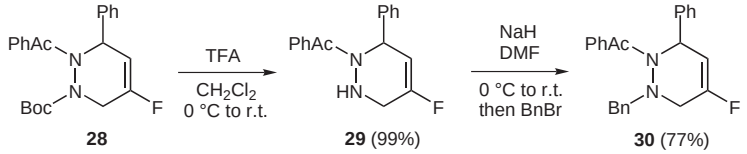
The hydrazines **15**–**17** were prepared starting from *tert*-butyl carbazate **12**, which was first condensed with benzaldehyde[7c] and then alkylated with vinylmagnesium bromide to give the Boc-protected hydrazine **14**. Advantage of this route is that different (aromatic) groups can be readily introduced, which as a bonus will significantly slow down the isomerization process. In order to orthogonally protect the hydrazine moiety, at this stage a number of different protecting groups were introduced on the second nitrogen atom which required extensive experimentation to reach reasonable selectivity and yields. For example, the Cbz group was introduced in 50% yield via deprotonation (NaH, –78 °C), followed by treatment with benzyl chloroformate and slowly warming to room temperature. Applying similar deprotonation conditions to the reaction with benzyl bromide led to mixtures of regioisomers. In this case, however, use of K_2CO_3 at 0 °C in combination with benzyl bromide, followed by adding KHMDS (1 equiv) and slowly warming to room temperature provided the desired product **16** in 36% yield. Finally, acylation of **14** with phenylacetyl chloride (PhAcCl) proceeded in acceptable yield (67%). In this case, PhAcCl was first reacted with Et_3N at 0 °C in THF for 30 minutes to form the corresponding ketene, which was then further reacted with **14** and slowly allowed to warm to room temperature overnight.

Functionalization of the second nitrogen proceeded uneventfully, starting with deprotonation of **15** in (NaH, THF, 0 °C to r.t.), followed by alkylation with **8** to give precursor **19** in 40% yield (entry 1, Table 1). The other alkylations, however, were carried out in DMF, which consistently gave higher yields. For example, deprotonation of **15** with NaH in DMF, followed by alkylation with commercially available 1-chloro-2-fluoroprop-2-ene (**18**) provided compound **20** in 70% yield (entry 2). Similar yields were obtained for precursors **21**–**23** using identical conditions (entries 3–5). All diolefinic hydrazines **19**–**23** were then subjected to the previously used RCM conditions (Grubbs II catalyst, toluene, 100 °C) as shown in Table 1. This led to the corresponding trifluoromethyl- or fluoro-substituted cyclic hydrazine building blocks **24**–**28** in reasonable to good yields. In almost all cases, 20 mol% of catalyst had to be added over a period of approximately 60 minutes in order to reach full conversion. Only in case of entry 2 somewhat less of the catalyst (15 mol%) appeared sufficient. This new synthetic pathway clearly establishes that RCM represents a viable pathway to obtain a novel class of cyclic hydrazine derivatives of potential biological relevance.

Table 1 RCM of *N*,*N*′-Dialkenylhydrazines

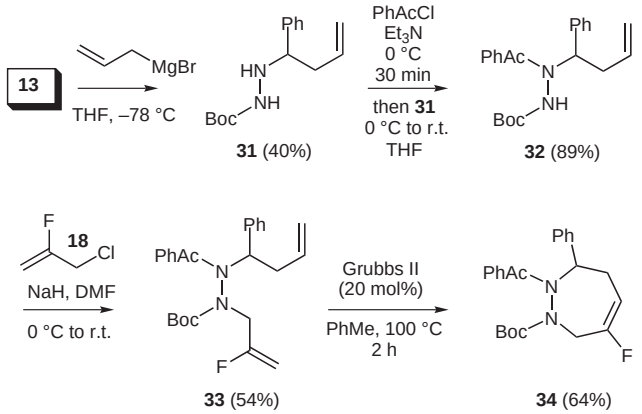
Entry	Precursor (yield)	Cat. (mol%)	Time (h)	Product (yield)
				
1	**19** X = CF_3 (40%)	20	1	**24** X = CF_3 (74%)
2	**20** X = F (70%)	20	1	**25** X = F (66%)
				
	21 (70%)	15	1	**26** (83%)
				
4	**22** X = CF_3 (76%)	20	1	**27** X = CF_3 (52%)
5	**23** X = F (70%)	20	1	**28** X = F (62%)

In order to show that the orthogonal protection can be exploited for further functionalization, the Boc group was replaced in a two-step procedure by a benzyl substituent (Scheme 4). This was realized via standard Boc deprotection of **28** with TFA, followed by benzylation of the resulting amine **29** (NaH in DMF at 0 °C, followed by BnBr) to give hydrazine **30** in 76% overall yield.



Scheme 4 Replacement of Boc with a benzyl substituent

Having successfully demonstrated that RCM readily leads to fluoro- and trifluoromethyl-substituted six-membered ring hydrazines, we decided to apply the same technique for the synthesis of a fluoride-containing seven-membered-ring hydrazine (Scheme 5).



Scheme 5 Synthesis of a fluorinated seven-membered-ring hydrazine

Thus, hydrazone **13** was reacted with allylmagnesium bromide to produce the Boc-protected hydrazine **31** in 40% yield.[14] The synthesis then proceeded as described previously, first selective acylation with PhAcCl via the intermediate ketene in 89% yield, followed by alkylation of resulting **32** with NaH and 1-chloro-2-fluoroprop-2-ene (**18**) to give RCM precursor **33** in 54% yield. The compound was then subjected to the standard RCM conditions (20 mol% Grubbs II catalyst added over a period of 2 hours, toluene, 100 °C) to afford the seven-membered-ring hydrazine **34** in a satisfactory yield of 64% along with a small amount of an unidentified side product. After chromatographic separation and subsequent crystallization, the identity of **34**, however, could be unambiguously established via X-ray crystallographic determination of the structure.[15]

In summary, an efficient and straightforward pathway for the synthesis of orthogonally protected fluorinateed cyclic hydrazines has been developed. Key step is the RCM-mediated ring closure of trifluoromethyl and fluoro-substituted olefins that lead to the corresponding cyclic products in reasonable to good yields. Considering the biological activity of cyclic hydrazines in general and the increasing role of fluorine in pharmaceutical products, this provides an entry into a potentially useful class of products.

Acknowledgment

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(14) **Representative Procedures**

***N*′-(1-Phenylbut-3-enyl)hydrazinecarboxylic Acid *tert*-Butyl Ester (31)**

Allylmagnesium bromide (4.57 mL of a 1.0 M solution in Et_2O, 4.57 mmol) was added at –78 °C to a well-stirred solution of **13** (336 mg, 1.53 mmol) in THF (2 mL). The mixture was stirred at –78 °C for 1 h and allowed over 12 h to reach r.t. It was poured into aq sat. NH_4Cl and the aqueous layer was extracted with Et_2O (3 × 6 mL). The ether layers were dried ($MgSO_4$), evaporated, and the crude product **31** (135 mg, 40%) was obtained as a colorless oil. IR (neat): 3403, 3283, 3067, 3028, 2980, 2928, 1709, 1455, 1368, 1282, 1243, 1156, 1022, 919, 759, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.31–7.24 (m, 5 H, Ph), 6.22, (s, 1 H, BocNH), 5.83–5.69 (m, 1 H, C*H*=CH_2), 5.13–5.03 (m, 2 H, CH=CH_2), 4.32 (br s, 1 H, PhC*H*), 4.11 (br s, 1 H, BocNHN*H*), 2.42–2.37 (m, 2 H, PhCHCH_2), 1.41 (s, 9 H, 3 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 156.6, 141.9, 134.7, 128.4, 127.8, 127.5, 117.9, 80.3, 63.3, 40.3, 28.4. ESI-HRMS: *m/z* calcd for $C_{15}H_{22}N_2O_2Na$ [M^+ + Na]: 285.1579; found: 285.15766.

***N*′-Phenylacetyl-*N*′-(1-phenylbut-3-enyl)hydrazine-carboxylic Acid *tert*-Butyl Ester (32)**

To a solution of phenylacetylchloride (64.8 μL, 0.5 mmol) in THF (2 mL), Et_3N (69.7 l, 0.5 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 30 min. At the same temperature compound **31** (130 mg, 0.51 mmol) was added and the mixture was allowed to reach r.t. over 12 h. The solvent was evaporated and the residue was purified using column chromatography (heptane–EtOAc, 10:1 to 6:1) to give **32** (166 mg, 89%) as a white solid; mp 107–109 °C. IR (neat): 3278, 3028, 2980, 2933, 1705, 1658, 1493, 1455, 1394, 1368, 1251, 1156, 707, 607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS, some signals appear as rotamers): δ = 7.40–7.14 (m, 10 H, Ar), 6.10 (br s, 1 H, NH), 5.88–5.52 (m, 2 H, C*H*Ph, CH_2=C*H*), 5.14–5.85 (m, 2 H, H_2C=CH), 3.72–3.63 (m, 2 H, CH_2Ph), 2.73–2.50 (m, 2 H, PhCHCH_2), 1.50 and 1.30 (s, 9 H, 3 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 165.2, 150.6, 145.2, 134.7, 130.8, 129.3, 129.1, 128.0, 127.8, 127.3, 126.9, 117.4, 81.9, 58.8, 49.2, 40.6, 28.4. HRMS (CI): *m/z* calcd for $C_{23}H_{29}N_2O_3$ [M^+ + H]: 381.2178; found: 381.2188.

***N*-(2-Fluoroallyl)-*N*′-phenylacetyl-*N*′-(1-phenylbut-3-enyl)hydrazinecarboxylic Acid *tert*-Butyl Ester (33)**

To a suspension of NaH (14 mg, 0.57 mmol) in DMF (5 mL) was added at 0 °C compound **32** (166 mg, 0.44 mmol). After stirring for 15 min at r.t., 1-chloro-2-fluoroprop-2-ene (**18**, 42 mg, 0.44 mmol) was added slowly. The reaction was stirred for 12 h, quenched with H_2O (5 mL) and extracted with Et_2O (3 × 5 mL). The ether layers were dried ($MgSO_4$), evaporated, and the residue was purified using column chromatography (heptane–EtOAc, 10:1) to give **33** (104 mg, 54%) as a colorless oil. IR (neat): 3062, 3032, 2976, 2928, 1718, 1679, 1497, 1450, 1364, 1251, 1156, 1031, 914, 854, 763, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS, some signals appear as rotamers): δ = 7.41–7.25 (m, 10 H, Ar), 5.65–5.43 (m, 3 H, CH_2=CH, CH_2=C*H*), 5.07–4.35 (m, 6 H, CH_2=CH, FC=CH_2, CHPh, NCH_2), 4.00–3.91 (m, 1 H, NCH_2), 3.72–3.54 (m, 2 H, CH_2Ph), 2.92 (br s, 2 H, PhCHCH_2), 1.42 and 1.22 (s, 9 H, 3 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, some signals appear as rotamers): δ = 173.8, 160.3 (d, *J* = 260.1 Hz, CF), 169.0, 134.3, 134.2, 133.8, 129.2, 129.1, 128.2, 127.8, 127.2, 126.3, 122.9, 95.5–95.2 (m, *C*H_2=CF), 82.2, 62.8, 39.8, 38.5, 37.5 (d, *J* = 48.8 Hz, *C*H_2CF), 27.8 and 27.3, HRMS (CI): *m/z* calcd for $C_{26}H_{32}N_2O_3F$ [M^+ + H]: 439.2397; found: 439.2389.

6-Fluoro-3-phenyl-2-phenylacetyl-2,3,4,7-tetrahydro[1,2]diazepine-1-carboxylic Acid *tert*-Butyl Ester (34)

To a solution of compound **33** (90 mg, 0.2 mmol) in anhyd toluene (40 mL) Grubbs II catalyst (20 mol%) was added at 100 °C in small portions over 2 h. The mixture was then evaporated and the product was purified using column chromatography (heptane–EtOAc, 10:1) to give **34** (52 mg, 64%) as a white solid; mp 110–113 °C. IR (neat): 3058, 3028, 2967, 2898, 2859, 1722, 1689, 1493, 1450, 1368, 1260, 1230, 1161, 1117, 1096, 1027, 858, 806, 698, 659, 517 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS, some signals appear as rotamers): δ = 7.37–7.08 (m, 10 H, Ar), 5.48 and 5.30 (br s, 1 H, CHPh), 5.30–4.86 (m, 1 H, CF=C*H*), 4.74 and 4.41 (d, *J* = 18.3, 1 H, NCH_2), 3.74–3.61 (m, 2 H, CH_2Ph), 3.22–3.12 (m, 1 H, NCH_2), 2.74–2.65 (m, 1 H, CH_2CHPh), 2.19–2.10 (m, 1 H, CH_2CHPh), 1.56 and 1.51 (s, 9 H, 3 CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, some signals appear as rotamers): δ = 173.7 and 173.4, 156.3 and 155.9 (d, *J* = 254.7 Hz, CF), 155.5 and 154.6, 141.5 and 141.3, 134.9 and 134.4, 129.2, 128.8, 128.7, 128.4, 127.3, 127.1, 126.9, 125.7, 101.2 and 100.6 (d, *J* = 18.9 Hz, *C*=CF), 83.5, 65.3 and 64.8, 50.2 and 48.6 (d, *J* = 42.8 Hz, NCH_2), 42.2 and 41.9, 28.3. HRMS (CI): *m/z* calcd for $C_{24}H_{28}FN_2O_3$ [M^+ + H]: 411.2084; found: 411.2075.

(15) Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 666813.