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Trapping *in situ* generated CF_3-nitrile imines with maleimides under solvent-free mechanochemical conditions†

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A series of trifluoromethylated pyrrolo[3,4-*c*]pyrazoles was obtained *via* mechanochemical (3 + 2)-cycloaddition of *in situ* generated trifluoroacetonitrile imines with maleimide and its *N*-aliphatic/aromatic analogues. The presented work demonstrated that the aforementioned 1,3-dipoles can be efficiently trapped with electron-deficient dipolarophiles under solvent-free ball-milling conditions.

There is increasing interest in applications of fluorinated nitrile imines for the synthesis of both heteroatom and heterocyclic systems,[1] and in this context, special attention has recently been paid to di- and trifluoroacetic acid analogues recognized as powerful building blocks for organofluorine synthesis.[2] The latter CF_3-nitrile imines **1** are readily available *in situ* by base-mediated dehydrohalogenation of the respective hydrazonoyl halides **2** (Scheme 1a), and they have been successfully applied for preparation of various five- and six-membered products including 1,3,4-thiadiazole,[3] 1,2,4-triazole,[4] pyrazoline and pyrazole,[5] as well as 1,3,4-thiadiazine[6] and 1,2,4-triazine derivatives,[7] available *via* formal (3 + 2)-cycloadditions or (3 + 3)-annulations, respectively.

In a series of recent reports, Huisgen cycloadditions of transient trifluoroacetonitrile imines **1** with suitable electron-deficient dipolarophiles leading to monocyclic as well as bicyclic (3 + 2)-cycloadducts, were demonstrated. For example, trapping of **1** with enones,[8] quinones,[9] nitro- and cyanoalkenes[10] in organic solutions is known; however, the mentioned transformations required rather longer reaction times (up to several days) and/or elevated temperatures (up to 90 °C) to afford reasonable amounts of the desired products. Thus, despite remarkable progress in exploration of nitrile imines **1** in reactions performed in solutions, development of alternative mild approaches, *e.g.* under ball-milling activation, is of general interest. Taking into account the well documented significance of pyrrolo-pyrazole scaffolds for drug discovery (Fig. 1),[11] here, we report (3 + 2)-cycloaddition reactions of CF_3-nitrile imines **1** with maleimides **3** leading to trifluoromethylated pyrrolo[3,4-*c*]pyrazoles **4** under solvent-free mechanochemical conditions (Scheme 1b).

We commenced our study with *N*-phenylmaleimide (**3a**) selected as a model dipolarophile and *N*-(4-tolyl)-trifluoroacetohydrazonoyl bromide (**2a**) applied as a precursor of the respective nitrile imine **1a** (Scheme 2). First, based on our experience in (3 + 2)-cycloaddition reactions of **1** with electron-deficient dipolarophiles, the designed reaction was briefly examined in solutions, to afford the expected pyrrolo[3,4-*c*]pyrazole **4a** in fair 81% yield under the optimized conditions (THF, 60 °C, 24 h, excess K_2CO_3). Notably, in contrast to previously reported cycloadducts of nitrile imines **1** with benzoquinones,[9] no spontaneous air-aromatization of **4a** could be observed and the final **4a** was obtained exclusively. The structure of the isolated bicyclic product **4a** was established on the basis of NMR data supplemented by MS measurements, while combustion analysis confirmed the molecular formula of **4a** as $C_{19}H_{14}F_3N_3O_2$ and the analytical purity of the sample. In ^{1}H NMR (600 MHz, $CDCl_3$) of **4a**, a set of two diagnostic absorptions located at $\delta = 4.80$ (dq, $^4J_{H-F} = 1.2$ Hz, $J_{H-H} = 11.5$ Hz) and $\delta = 5.41$ (d, $J_{H-H} = 11.5$ Hz), attributed to 3a-H and 6a-H, respectively, confirmed the relative *cis*-configuration of the obtained bicyclic product. As expected, two characteristic quartets

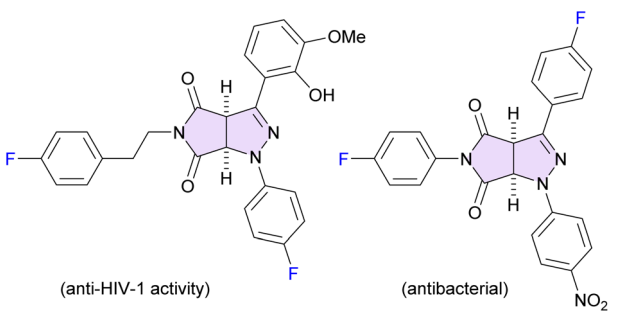

Fig. 1 Exemplary fluorinated bioactive pyrrolo[3,4-*c*]pyrazoles.

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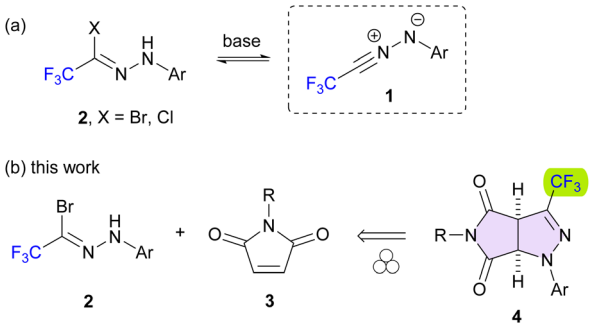
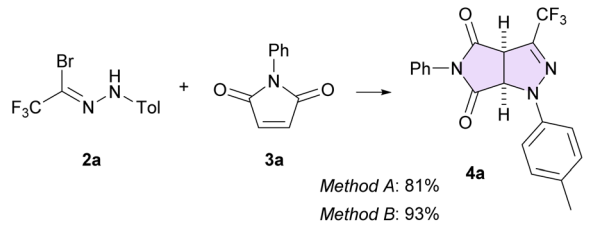


Scheme 1 (a) Base-induced generation of CF_3-nitrile imines **1** and (b) the mechanochemical (3 + 2)-cycloadditions of **1** with maleimides reported herein.

at $\delta = 120.2$ ($^1J_{C-F} = 270.0$ Hz) and $\delta = 131.3$ ($^1J_{C-F} = 39.8$ Hz) attributed to the CF_3 group and the C(3) atom of the core heterocycle were found in the ^{13}C NMR (151 MHz, $CDCl_3$) of **4a**.

Initial mechanochemical experiments were carried out using equimolar amounts of starting materials **2a** and **3a**, in a ball-mill, using a 5 mL stainless steel vessel (one steel ball, ø 7 mm, 22 Hz), and a series of organic (Et_3N and DABCO) and inorganic (KF, CsF, Na_2CO_3, K_2CO_3, and Cs_2CO_3) bases was checked to indicate nearly complete conversion (96%) and a high isolated yield of 85% in the case of K_2CO_3 (1.2 equiv.) used for the dehydrohalogenation step, after 90 min of grinding (see the ESI†). Further optimization with respect to diameter and number of milling balls (ø 3, 5 or 7 mm; up to 3 balls) showed no remarkable changes, whereas the use of a slight excess of the nitrile imine precursor **2a** (1.1 equiv.) was found to be beneficial and provided the target cycloadduct **4a** almost quantitatively (100% conversion; 93% isolated yield).§

With optimized conditions in hand, a series of solid hydrazonoyl bromides **2b–2g** was subjected to neat grinding with *N*-phenylmaleimide (**3a**) to provide the expected (3 + 2)-cycloadducts **4b–4g**, which were generally isolated in high yield (80–95%; Fig. 2). However, in certain cases a prolonged reaction time was necessary to lead the reaction to completion (for details, see the ESI†); for example, in the case of the nitrile imine precursors **2f** and **2g** bearing strongly electron-withdrawing substituents (two Cl atoms and a CN group, respectively) attached to the phenyl ring, ball-milling for 10 h (for **2f**) and 18 h (for **2g**), assured complete consumption of starting materials. Noteworthily, neither **2f** nor cycloadduct **2g** could be obtained in solution according to Method A reported for model Tol-functionalized pyrrolo[3,4-*c*]pyrazole **4a**. Only in



Scheme 2 Synthesis of pyrrolo[3,4-*c*]pyrazole **4a**. Method A: **2a** (1.25 equiv.), K_2CO_3 (5.0 equiv.), THF, 60 °C, 24 h; Method B: **2a** (1.1 equiv.), K_2CO_3 (1.1 equiv.), ball-milling (5 mL jar, one steel ball ø 7 mm), rt, 90 min.

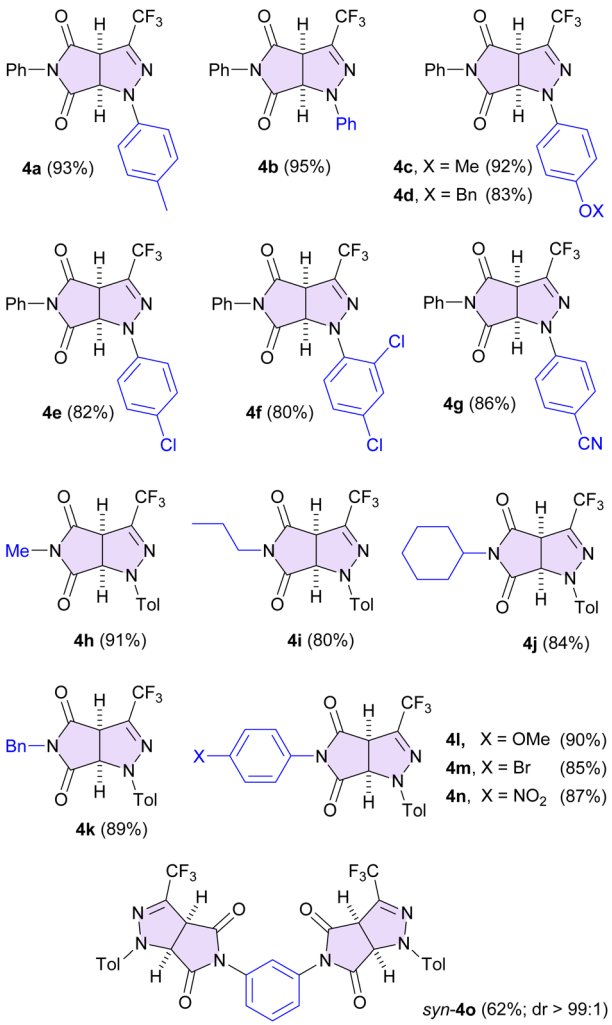


Fig. 2 Scope of trifluoromethylated pyrrolo[3,4-*c*]pyrazoles **4a–4o**.

§ General procedure for synthesis of **4**: solid hydrazonoyl bromide **2** (1.1 mmol), solid maleimide **3** (1.0 mmol), and solid K_2CO_3 (1.2 mmol, 166 mg) were placed in a 5 mL stainless steel grinding jar with one stainless steel ball (7 mm diameter). The jar was closed and ball-milled at 22 Hz until the starting maleimide was fully consumed. Then, CH_2Cl_2 (10 mL) was added, the precipitate was filtered, washed with CH_2Cl_2 (2 × 10 mL), and the solvent was removed *in vacuo*. The crude product **4** was purified by filtration through a short silica gel pad (FCC), standard column chromatography (CC) or recrystallized. 5-Phenyl-1-(*p*-tolyl)-3-trifluoromethyl-3a,6a-dihydropyrrolo[3,4-*c*]pyrazole-4,6(1*H*,5*H*)-dione (**4a**): reaction time 90 min; FCC (SiO_2, petroleum ether/DCM 1 : 1); colorless solid, 347 mg (93%); mp 169–170 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.80 (dq, $J = 1.2$, 11.5 Hz, 1H), 5.41 (d, $J = 11.5$ Hz, 1H), 7.16–7.19 (m, 2H), 7.29–7.31 (m, 2H), 7.42–7.50 (m, 5H). $^{13}C\{1H\}$ NMR (151 MHz, $CDCl_3$) δ 20.8, 52.2, 66.4, 115.2, 120.2 (q, $^1J_{C-F} = 270.0$ Hz), 126.3, 129.4, 129.5, 130.0, 131.0, 131.3 (q, $^2J_{C-F} = 39.8$ Hz), 133.1, 140.3, 169.1, 170.7. ^{19}F NMR (565 MHz, $CDCl_3$): δ −63.6 (s, CF_3). IR (neat) ν 1722, 1514, 1498, 1379, 1320, 1193, 1122, 1077, 1040 cm^{-1}. (−)-ESI-MS (*m*/*z*): 372.1 (100, $[M - H]^-$). Anal. calcd for $C_{19}H_{14}F_3N_3O_2$ (373.3): C 61.13, H 3.78, N 11.26; found: C 61.13, H 3.77, N 11.24.

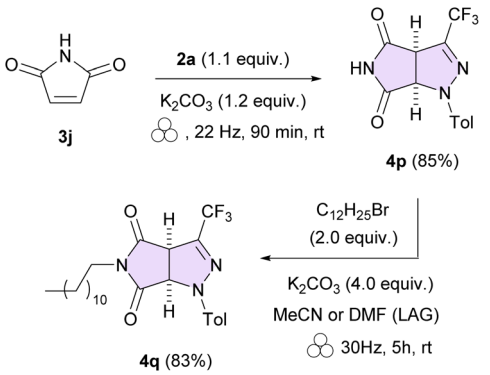
the case of *p*-nitrophenyl-functionalized hydrazonoyl bromide of type **2** no desired product could be obtained under mechanochemical conditions; NMR analysis of the crude reaction revealed a low consumption of maleimide **3a** (<10%) even after 48 h of ball-milling. In addition, partial decomposition of the starting nitrile imine precursor, leading to a complex mixture, was observed.

The scope of maleimides was also checked, and a series of selected solid *N*-(cyclo)alkyl (**3b–3d**) and *N*-aryl-substituted (**3f–3h**) analogues was examined in mechanochemical (3 + 2)-cycloaddition with bromide **2a** (Fig. 2). Similar to the result noticed for the model compound **4a**, in all reactions complete consumption of the starting materials was observed in a reasonable reaction time of 90 min, irrespective of the steric and electronic character of the *N*-substituent in maleimide. For example, Me- (**4h**, 91%) and *c*Hex- (**4j**, 84%), as well as *p*-$MeOC_6H_4$- (**4l**, 90%) and *p*-$NO_2C_6H_4$- (**4n**, 87%) analogues were isolated as spectroscopically pure materials by simple filtration through a short silica gel pad.

Next, 1,3-phenylene bis-maleimide **3i** was involved in the study to provide the corresponding product **4o** (62%) resulting from double (3 + 2)-cycloaddition, and the analysis of the ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of the mother liquor revealed the formation of a single diastereomeric product (dr > 99 : 1). According to the literature, double cycloadditions of bis-imide **3i** can either lead to products of C_2-symmetry (*anti*-addition)[12a,b] or to *syn*-configured[12c,d] materials. To get more information about the structure of **4o**, the isolated product was analysed by NMR spectroscopy in the presence of (–)-(*R*)-mandelic- and (+)-(*R*)-(*tert*-butyl)(phenyl)phosphonothioic acids selected as chiral solvating agents (in 1 : 1 and 1 : 2 ratios of **4o** : additive, respectively).[13] In all four measurements a single set of signals attributed to **4o** was found in ^{1}H NMR spectra. Furthermore, HPLC analysis of **4o** by using a chiral stationary phase (Chiralcel OD) provided a single fraction of the product. Thus, based on the above experiments the *meso* structure of **4o** resulting from *syn*-addition of the second nitrile imine molecule **1a** was tentatively proposed (Fig. 2).

To check whether the *N*-unsubstituted pyrrolo[3,4-*c*]pyrazoles of type **4** can also be accessed by the devised mechanochemical approach, the model hydrazonoyl bromide **2a** was treated with maleimide (**3j**) (Scheme 3). Gratifyingly, the desired product **4p** was formed in a highly chemoselective manner, and was isolated in 85% yield, although the formation of small amounts of unidentified intermolecular by-products was also detected. Possibly, the competitive reaction initiated by nucleophilic attack of the N atom of maleimide onto the positively charged C-termini of the 1,3-dipole **1a** takes place, analogous to a recent report by Madabhushi on reactions of classical *C*,*N*-diaryl nitrile imines with succinimide;[14] however, attempted isolation of by-product(s) by standard column chromatography was unsuccessful.

Subsequent functionalization of **4p** with dodecyl bromide, selected as an exemplary oleophilic electrophile, was carried out under standard alkylation conditions, *i.e.* in MeCN solution (K_2CO_3, 60 °C, 16 h), and provided the expected material **4q** (87%) as a sole product. Furthermore, prompted by the work by



Scheme 3 One-pot telescopic mechanochemical synthesis of pyrrolo[3,4-*c*]pyrazole **4q** through (3 + 2)-cycloaddition of **2a** with maleimide (**3j**) and subsequent alkylation of the first formed cycloadduct **4p**.

Margetić dealing with mechanochemical alkylations of imides,[15] we examined the solvent-free one-pot telescopic approach towards **4q**. To our delight, treatment of the initially formed crude (3 + 2)-cycloadduct **4p** with excess $C_{12}H_{25}Br$ (2.0 equiv.) in the presence of K_2CO_3 (10.0 equiv.) opened up access to the final compound under exclusive mechanochemical activation; however, addition of either MeCN or DMF as a liquid assisted grinding solvent ($\eta = 0.35$ μL mg^{-1}) was found to be essential as no desired product could be obtained under simple neat grinding.

Conclusions

In conclusion, an operationally simple and highly efficient protocol for the mechanochemical synthesis of trifluoromethylated pyrrolo[3,4-*c*]pyrazoles by trapping of CF_3-nitrile imines with maleimides is reported. The presented results indicate that hydrazonyl halides can serve as suitable precursors for *in situ* generation of the corresponding nitrile imines under solvent-free ball-milling conditions. Of note, the remarkable decrease in reactivity with increasing electron-deficient character of the substituent located at the N-termini of the starting hydrazonoyl halide was observed. On the other hand, a series of *N*-functionalized maleimides bearing (cyclo) alkyl groups or variously substituted phenyl substituents reacted smoothly with the model 1,3-dipole. Finally, the parent maleimide lacking substituent at the N atom was successfully applied for one-pot telescopic (3 + 2)-cycloaddition followed by *N*-alkylation under mechanochemical conditions. The devised approach supplements hitherto reported classical methods for the synthesis of fluorinated and non-fluorinated pyrrolo[3,4-*c*] pyrazoles of interest in the context of chemical biology applications.[11,12b,16]

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

GUJ & SJ: conceptualization, methodology, investigation, and data processing. MJ: conceptualization, supervision, writing, review, and editing.

Conflicts of interest

There are no conflicts to declare.

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