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Concise preparation of 8-trifluoromethyltetrahydro-6*H*-pyrido [1,2-*a*] pyrazine-6-one ☆

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ABSTRACT

Methodology to rapidly and efficiently assemble 8-trifluoromethyltetrahydro-6*H*-pyrido [1,2-*a*] pyrazine-6-one (**11**) has been developed and its general applicability has been demonstrated.

We recently disclosed the preparation of MK-0812 (Fig. 1), a potent chemokine (CCR2) receptor antagonist containing four chiral centers and featuring a tetrahydro-3-trifluoromethyl-1, 6-naphthyridine nucleus.[2] Ongoing issues related to pharmacokinetic and ion-channel activities required further elaboration of this structural class. We surmised that perhaps the inclusion of more polar heterocycles such as that in analog **1** would be the most promising area for further investigation.

Scheme 1 illustrates the original route used to access the target heterocycle **11**[3] that was required for the synthesis of **1.** From the commercially available 2, 6-dichloro-4-trifluoromethylpyridine (**2**), a successive introduction of a *tert*-butoxy group (**3**) then a cyano group, led to **4**. Reduction of the cyano function by catalytic reduction to give **5** was followed by sulfonylation of the primary amine to afford **6**. A two-step sequence of reactions involving the alkylation of the sulfonamide **6** with 1,2-dibromoethane gave **7** which was followed by cleavage of the *tert*-butoxy group to afford **8**. Base-induced facile ring closure of **8** yielded **9**. The 2-nitrophenylsulfonyl group in **9** was removed under standard conditions and the final purification was aided by the temporary introduction of a Boc-carbamate protecting group to initially afford **10** which was then transformed to **11**.

Unfortunately, the starting material **2** was difficult to obtain in large quantities[4] and an alternative route to **11** was investigated. We envisioned that a suitably functionalized ynoate such as **12**, could initially undergo an intramolecular conjugate addition of the amino group to the triple bond[5] to yield a piperazine derivative **13**, and the heterocycle **9** would then form in a spontaneous ring closure as shown in Figure 2.

The requisite hydrochloride salt of ynoate **12** was prepared as illustrated in Scheme 2. Reaction of commercially available mono-*N*-Boc-ethylenediamine (**14**) with 2-nitrobenzenesulfonyl chloride[6] gave the sulfonamide **15**. Its N-alkylation with propargyl bromide afforded the intermediate **16**, which was coupled to the iodoester **17**[7] under Sonogashira conditions[8] to afford ynoate **18**. Cleavage of the Boc-protecting group produced the amine **12** as a hydrochloride salt.

From the many possible metal catalysts that might trigger the desired cyclization**,** we chose mercury, since this catalytic system has been well studied in similar instances.[9,10] Indeed, exposure of **12** to catalytic amounts of mercury(II) chloride at elevated temperature induced a smooth cyclization, and the key intermediate **9** was obtained in high yield whose spectral data matched those of similar analog prepared as described in Scheme 1. It was then subsequently converted to **11** as described in Scheme 1.

When the key cyclization of **12** to **9** was performed in the absence of a catalyst, the reaction was found to be sluggish requiring several hours to complete.[11] To gain a deeper understanding of this cascade reaction, a mechanistic study using high-resolution NMR spectroscopy was undertaken. The key findings are summarized in Scheme 3.

The hydrochloride salt of amine **12** was dissolved in dioxane-d_8 and a stoichiometric amount of triethylamine-d_{15} was added, and the reaction progress was monitored at ambient temperature by ^{1}H NMR. The initial spectrum of **12** changed within minutes to an intermediate that was assigned structure **19**. Subsequently, the intermediate **19** was found to convert to the final product **9** over a period of 2 days at room temperature.

The structure of the key intermediate **19** was assigned as follows: Isomeric structure **21** was eliminated because the NMR spectrum clearly indicated a presence of only one vinyl proton along with four aliphatic methylene groups. Structures **19** and **20**, both consistent with this NMR pattern, were distinguished based on 3-bond ^{1}H–^{13}C correlation between the proton H-e and the ester carbonyl C-j (HMBC). A strong NOE between H-a and H-d provided further support for structure **19**. In addition, the stereochemistry of

☆ See Ref. 1.

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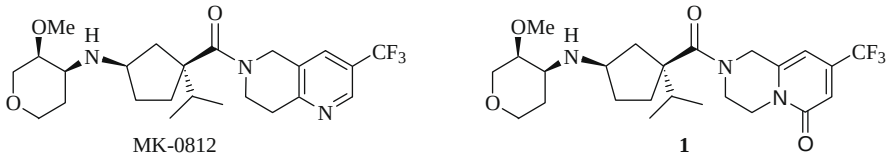
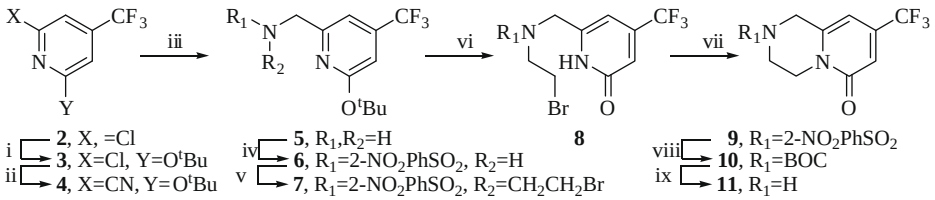


Figure 1.



Scheme 1. Reagents and conditions: (i) KO^{t}Bu, THF, 0 °C; (ii) $Zn(CN)_2$, $(PPh_3)_4Pd$, DMF, 90 °C; (iii) H_2, RaNi, EtOH; (iv) 2-nitrophenylsulfonyl chloride, DIEA, DCM; (v) 1,2-dibromoethane, K_2CO_3, DMF; (vi) TFA, rt, 10 min; (vii) K_2CO_3, THF, 60 °C; (viii) (a) PhSH, K_2CO_3, DMF; (b) BOC_2O, K_2CO_3, DMF; (ix) HCl.

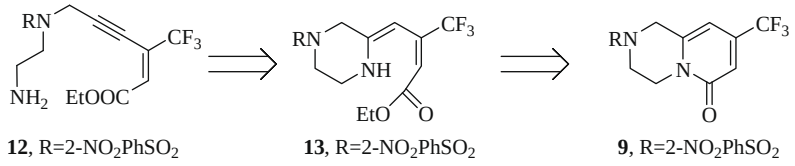
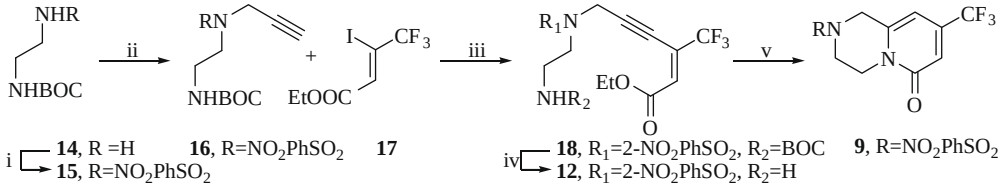
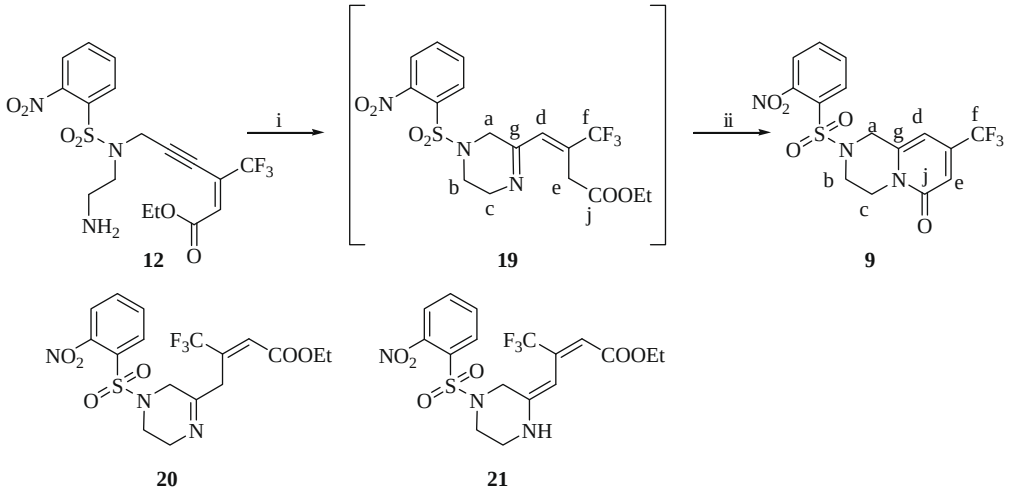


Figure 2.



Scheme 2. Reagents and conditions: (i) 2-nitrobenzenesulfonylchloride, CH_2Cl_2, TEA, 100%; (ii) propargyl bromide, K_2CO_3, DMF, 0 °C to rt, 96%; (iii) $PdCl_2(PPh_3)_2$, CuI, TEA, THF, 70 °C, 71%; (iv) HCl, EtOAc, 0 °C to rt, 94%; and (v) $HgCl_2$ (10 mol %), TEA, dioxane, 60–70 °C, 83%.



Scheme 3. Reagents and conditions: (i) **12**·HCl, dioxane-d_8, TEA-*d15*, rt, (ii) dioxane-d_8, rt, 48 h.

Table 1
Select ^{13}C and ^{1}H NMR chemical shifts of **19** and **9**[a]

Position	19		**9**	
	^{13}C	^{1}H	^{13}C	^{1}H
a	47.3	3.91	45.4	4.53
b	40.7	3.27	43.6	3.68
c	49.5	3.83	40.5	4.11
d	129.4	6.58	97.9	6.32
e	32.2	3.61	115.8	6.75
g	159.4	—	144.9	—
j	168.2	—	160.5	—
CF_3	124.6	—	124.5	—

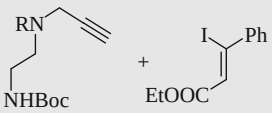
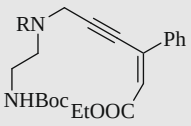
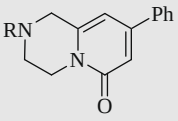
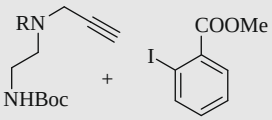
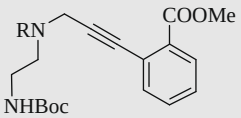
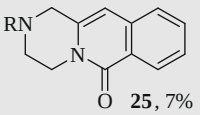
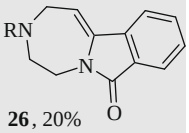
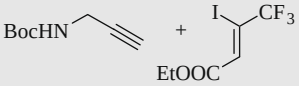
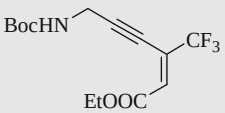
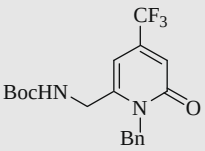
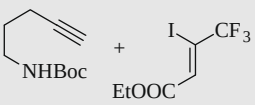
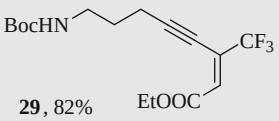
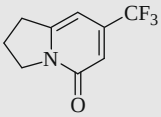
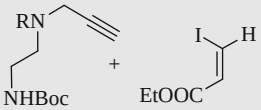
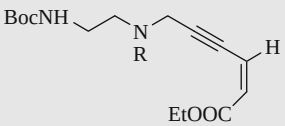
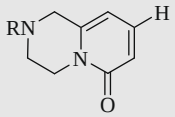
[a] In dioxane-d_8, 600 MHz.

the double bond was determined to be *E* based on a strong ^{19}F–^{1}H NOE between the trifluoromethyl group and H-d. Based on this evidence we postulate that the cyclization precursor **12** was initially transformed to **19** which over time produced the final bicycle **9**. The key NMR characteristics of compounds **19** and **9** are summarized in Table 1.

The cascade cyclization approach described for the conversion of **12** to **9** has been extended to other systems. These results are summarized in Table 2.[12]

The efficient transformation of **22** to **23** illustrates that the phenyl group can be a replacement for a trifluoromethyl group during this cyclization. A non-regioselective cyclization of **24** led to the fused heterocycle **25** and its regioisomer **26** thus demonstrating the potential to expand this methodology to linear tricyclic heterocycles, low yields not withstanding. We also show that this cyclization reaction can be performed in an intermolecular manner that involves an external nucleophile (in the present case with benzyl amine) as exemplified by the transformation of **27** to afford **28** in a respectable yield. Pyridones such as **28** with aminomethyl

Table 2
Extension of cascade cyclization to other systems[a,b,c]

Entry	Starting materials[d,e]	Coupling product	Cyclization product
1		 **22**, 47%	 **23,** 58%
2		 **24**, 85%	 **25**, 7% +  **26**, 20%
3[f]		 **27**, 51%	 **28**, 73%
4		 **29**, 82%	 **30**, 82%
5		 **31**, 38%	 Product Not formed

[a] Isolated yields of pure products that have been characterized by high-resolution NMR/MS.
[b] Experimental conditions were similar to the one discussed for the transformation of **12** to **9**.
[c] Yields not optimized.
[d] Reaction performed in accordance with Ref. 7.
[e] R = 2-nitrobenzenesulfonyl.
[f] The cascade cyclization involved benzylamine as an external nucleophilic source.

appendages are very hard to prepare by other methodologies. The cyclization of **29** to **30** offers the possibility to expand on the scope of this reaction further to give fused pyridones. Finally, the substrate **31** surprisingly, which lacks substitution at the double bond, was rapidly consumed but none of the desired product was formed, and the reasons for this failure are not clear.

In conclusion, a highly efficient cascade cyclization pathway that greatly improves the access to an important class of fused and bridged heterocycles has been developed. We believe that the present methodology has a significant scope and enormous potential for the rapid generation of pharmacologically important heterocycles.

Supplementary data

Supplementary data (procedure, NMR data for the mechanism and for the intermediates **9**, **12**, **14–19**, and **22–31**) have been provided.

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10. *General procedures*: *Preparation of* (**18**): To a suspension of alkyne **16** (17.3 g, 45.14 mmol) in anhydrous THF (125 ml) was sequentially added vinyl iodoester **17**[7] (14.6 g, 49.65 mmol), copper (I) iodide (0.89 g, 4.51 mmol), $Pd[(Ph_3P)_3]_4$ (2.62 g, 2.26 mmol), and potassium carbonate (24.95 g, 180.56 mmol) under nitrogen. The resulting reaction mixture was stirred at 70 °C for 5 h, filtered, concentrated, and flash chromatographed (hexane + 15–25% ethyl acetate) to give **18** (17.69 g, 71%) as an oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00–8.02 (m, 1H), 7.64–7.59 (m, 3H), 6.55 (s, 1H), 4.69 (b,1H), 4.52 (s, 2H), 4.18 (q, J = 6.1 Hz, 2H), 3.55–3.58 (t, 2H), 3.36–3.38 (t, 2H), 1.39 (s, 9H), 1.24–1.30 (t, J = 6.1 Hz, 3H). LC–MS for $C_{22}H_{26}F_3N_3O_8S$ $[M+H]^+$ calcd 550.14, found 450.05, (*m*-100, loss of *t*-butoxy group).
Preparation of (**12**): To a stirred solution of the *N*-Boc-protected amine **18** (17.69 g, 32.19 mmol) in EtOAc (100 ml) at 0 °C was added a saturated solution of HCl (g)/ethyl acetate (200 ml). The reaction mixture was stirred at 0 °C for an additional 2 h after which it was concentrated to give the hydrochloride salt of **12** (14.7 g, 94%) as a tan crystalline solid. LC–MS for $C_{17}H_{18}F_3N_3O_6S$ $[M+H]^+$ calcd 450.09, found 450.05.
Preparation of (**9**): A stirred solution of alkyne **12** (14.6 g, 30.04 mmol) in anhydrous 1, 4 dioxane (100 ml) was treated with mercury(II) chloride (0.81 g, 3.00 mmol) and triethylamine (8. 22 ml, 60.08 mmol) under nitrogen. The resulting suspension was then gently heated at 65 °C for 30 min, concentrated, and flash chromatographed (methyl-*t*-butylether + 15–35% ethyl acetate) to afford **9** (10.09 g, 83%) after trituration with diethyl ether. LC–MS for $C_{15}H_{12}F_3N_3O_5S$ $[M+H]^+$ calcd 404.04, found 404.05.
11. Longer reaction time inevitably also led to lower yields in addition to intractable mixtures of products.
12. Cyclization procedure to afford the products (**23**, **25**, **26**, **28**, and **30**) was very similar to the one discussed for **19** to **9** in Ref. 10.