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Tetrahydrocarbazoles by mechanochemical Fischer indolisation

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ABSTRACT

The Fischer indolisation (FI) typically proceeds in the presence of a Brønsted or Lewis acid in an organic solvent at elevated temperatures. Herein, we report that tetrahydrocarbazoles (THCs) are accessible by mechanochemical FI at ambient temperature. Using phenylhydrazine hydrochlorides in the presence of silica is critical for this solid-state variant of the FI.

Introduction

Tetrahydrocarbazoles (THCs) are privileged heteroaromatic scaffolds present in a variety of compounds with a range of biological properties [1] (Fig. 1). For example, THCs are present in the anti-emetic ondansetron, [2] the migraine treatment frovatriptan [3] and experimental therapeutics in advanced stages of clinical trials, including the BTK inhibitor BMS-986142 [4] and the PET tracer flutriciclamide F18 [5]. A large number of natural products also contain the THC scaffold [6–9].

A reliable and very commonly employed method for the synthesis of THCs is the Fischer indolisation (FI), a timeless reaction with an array of applications in industry and academia (Scheme 1). [10] Despite being an exemplar method for constructing indoles, the FI typically requires a Brønsted acid (e.g., HCl, H_2SO_4, TFA, *p*-toluenesulfonic acid) [11] or Lewis acid (e.g., BF_3, $ZnCl_2$, $AlCl_3$) [12] in organic solvents at elevated temperatures. As a result, the FI is energy-intensive and generates large amounts of waste.

Results and discussion

The development of greener FIs has focused on heterogeneous and recyclable acid catalysts (zeolites, montmorillonite clays, etc.) [13], environmentally friendly solvents [14], and flow chemistry methods [15]. To the best of our knowledge, there are no reports of the FI being conducted using mechanochemistry, an emerging synthesis technique that adheres to many green chemistry principles [16–18]. Accordingly, we instigated a programme to examine if the FI was compatible with mechanochemistry, specifically targeting the THC scaffold. Phenylhydrazine hydrochloride (**1**) and cyclohexanone (**2**) were ball-milled at 400 rpm, but no THC (**3**) was observed (Table 1, Entry 1). Several different grinding auxiliaries [19] were screened; addition of sodium chloride, sodium sulfate and alumina (basic and neutral) all resulted in no reaction (Entries 2–5). Pleasingly, upon addition of silica, THC (**3**) was obtained in a respectable yield (Entry 6). Reducing the amount of silica by half (0.5g) led to a noticeable reduction in yield (Entry 7), while doubling the mass added (2.0 g) had little effect (Entry 8). The addition of acidic silica was vital, as both neutral (Entry 9) and pyrogenic silica [20] (Entry 10) did not promote the reaction. Interestingly, when phenylhydrazine free base was used as the substrate, the reaction failed (Entry 11). Clearly, the presence of both the HCl and silica is vital to the solid-state FI's success – if either is absent, the reaction fails. The exact mechanism of this process is not clear, but it is possible that the HCl adsorbs onto the silica, generating acidic surfaces that promote the FI. Investigations into this process are ongoing.

Next, an optimisation study focusing on reaction time and milling speed was undertaken (Table 2; entry 1 represents the best conditions discovered during the auxiliary screen). Reducing the milling speed to 300 rpm led to no reaction (entry 2). Shortening the reaction time at 400 rpm significantly decreased the yield (entry 3), while increasing the reaction time led to a significant increase (entries 4 and 5). Attempts to replicate the high yields under shorter reaction times by increasing the milling speed were partially successful (entries 6–13); at 600–

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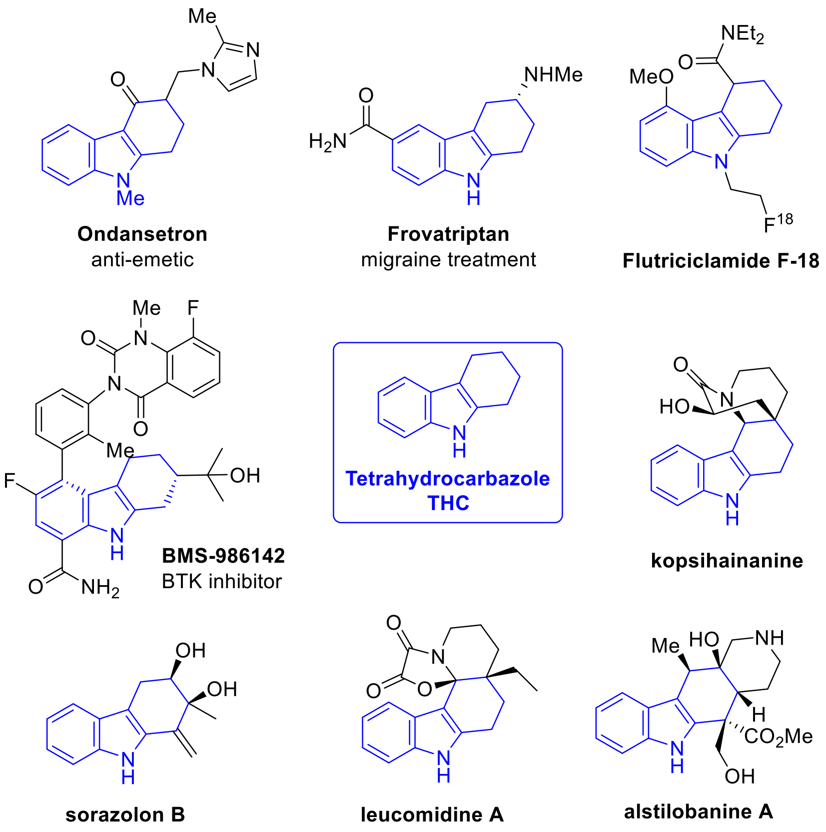
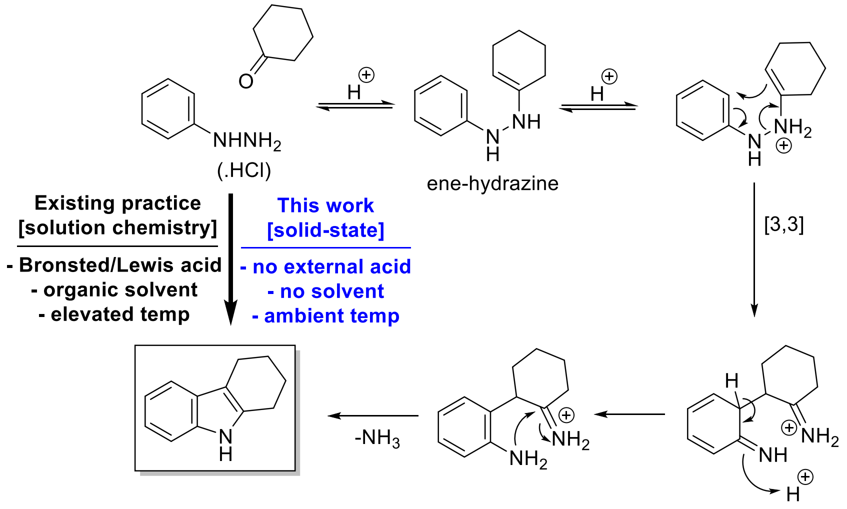


Figure 1. THCs present in approved therapeutics, investigational medicines, and natural products.

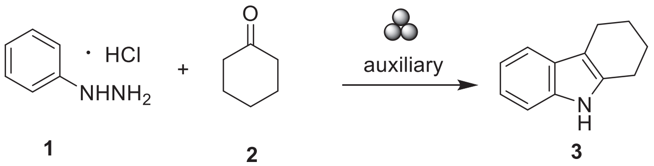


Scheme 1. Synthesis of tetrahydrocarbazoles (THCs) by Fischer indolisation (FI).

650 rpm, degradation occurred at reaction times longer than those stated in Table 2.

The solid-state FI scope was investigated using a series of commercially available phenylhydrazine hydrochlorides and cyclohexanones (Scheme 2). All the reactions were performed at 600 rpm as the optimisation study indicated this resulted in shorter reaction times. 6-Fluoro-, 6-bromo- and 6-chlorotetrahydrocarbazoles (**4**–**6**) were readily accessible, demonstrating that halogenated phenylhydrazines are compatible with this process. 6-Methyltetrahydrocarbazole (**7**), 8-ethyltetrahydrocarbazole (**8**) and 5,7-dimethyltetrahydrocarbazole (**9**) were accessible, showing that *para*-, *ortho*- and *meta*-alkylphenylhydrazines are viable reactants. Alkylcyclohexanones are compatible with this process, as exemplified by the synthesis of THCs **10**–**13**. The fluorinated THCs **14**/**15**

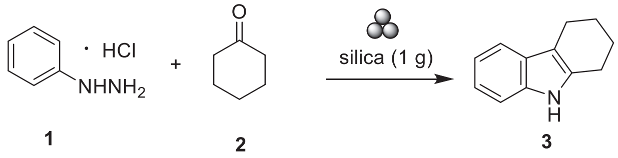
Table 1
Effect of auxiliaries on the solid-state FI.[a,b]



Entry	Auxiliary (g)	Time (h)	rpm	outcome
1	none	1	200–600	no reaction
2	NaCl (1)	0.5	200–600	no reaction
3	Na_2SO_4 (1)	0.5	200–600	no reaction
4	neutral alumina (1)	0.5	200–600	no reaction
5	basic alumina (1)	2	200–600	no reaction
6	**silica (1)**	**4**	**400**	**58%**
7	silica (0.5)	4	400	28%
8	silica (2.0)	4	400	54%
9	neutral silica (1)	4	400–500	no reaction
10	pyrogenic silica (1)	4	400–500	no reaction
11[c]	silica (1)	1–10	200–600	no reaction

[a] Auxiliary was added to phenylhydrazine.HCl (1.38 mmol) and cyclohexanone (1.38 mmol) in a 12 mL stainless steel jar filled to 1/3 capacity with 5 mm stainless steel balls. [b]All reactions conducted in a Retsch PM 100 planetary ball-mill. [c]$PhNHNH_2$ used instead of $PhNHNH_2$.HCl. rpm = revolutions per minute.

Table 2
Effect of milling speed and reaction time and on the solid-state FI synthesis of tetrahydrocarbazole (3)



Entry	Time (h)	rpm	Yield 3 (%)
1	4	400	58
2	2	300	no reaction
3	3	400	28
4	8	400	88
5	10	400	95
6	1	500	28
7	2	500	30
8	3	500	42
9	5	500	64
10	2	600	68
11	3	600	80
12	4	600	70
13	3	650	56

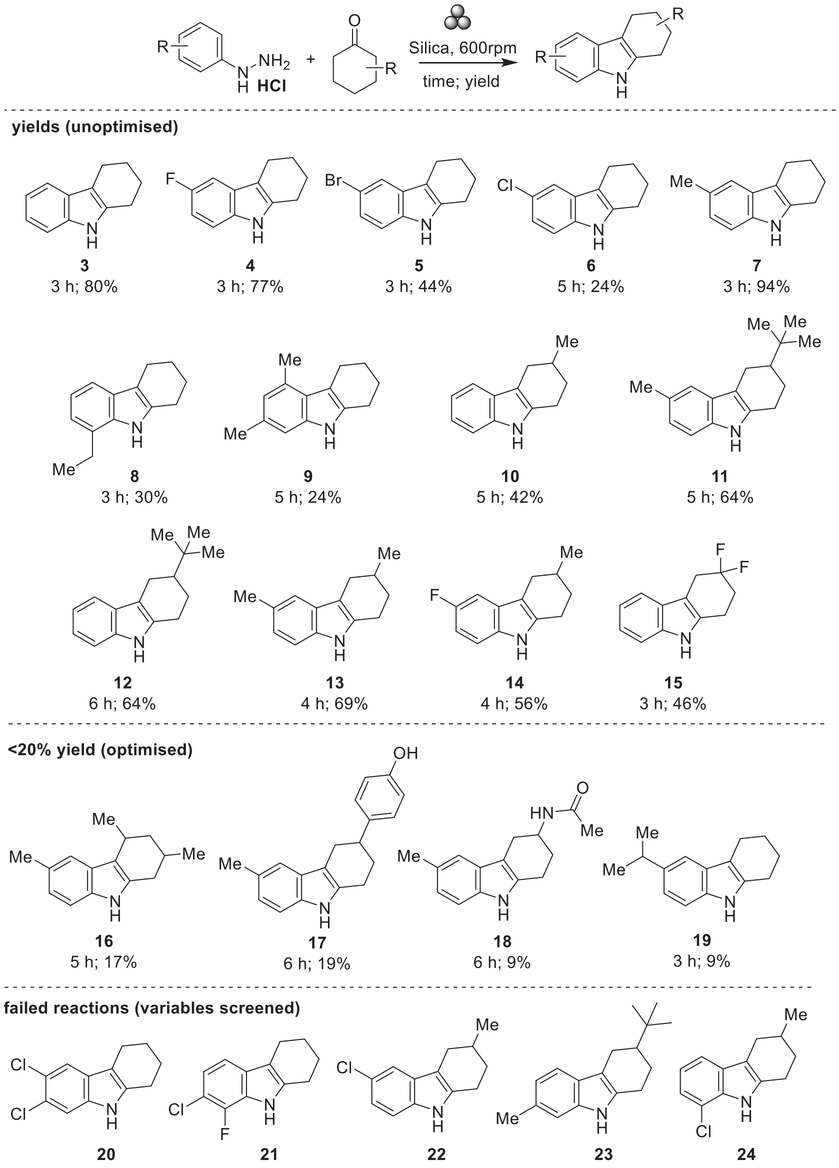
Phenylhydrazine.HCl and cyclohexanone were added in equimolar amounts (1.38 mmol) to silica (1 g) in a 12 mL stainless steel jar filled to 1/3 capacity with 5 mm stainless steel balls. All reactions were conducted in a Retsch PM 100 planetary ball-mill. rpm = revolutions per minute.

were readily accessible, important examples given the utility of fluorine in medicinal chemistry settings. [21] Several THCs (**16**–**19**) were formed in low yield (<20%), while other FIs failed altogether (**20**–**24**).

In the examples where yields were low (<20%) or the reaction failed altogether, there does not appear to be a clear steric or electronic reason to support these outcomes. However, in the lower yielding reactions, competing degradation pathways are clearly apparent (TLC and ^{1}H NMR analysis of the crude reaction mixture). Thus, it appears the success of the solid-state FI is reliant on the stability of the reaction components during ball-milling. This is unsurprising as ball-milling has emerged as an effective technology for the destruction of environmentally-persistent organic pollutants [22]. To determine if a specific FI is compatible with a solid-state process, the stability of the individual reactants can be readily ascertained upon milling a small sample with silica, a practice we now routinely employ in our laboratory.

Conclusions

In summary, a solid-state FI between phenylhydrazine hydrochlorides and cyclohexanones occurs in the presence of silica at ambient temperature to give THCs in variable yields. The success of this reaction is reliant on both silica and HCl (from the phenylhydrazine salt) being present, inferring the reaction may be promoted by acidic surfaces resulting from adsorption of HCl onto the silica. This clean process provides an alternative to a widely employed heteroannulation reaction typically reliant on Brønsted/Lewis acids, organic solvents and elevated temperatures.



Scheme 2. Solid-state synthesis of THCs. [a]Phenylhydrazine.HCl and cyclohexanone were added in equimolar amounts (1.38 mmol) to silica (1 g) in a 12 mL stainless steel jar filled to 1/3 capacity with stainless steel balls (5 mm; 14.6 g total). All reactions conducted in a Retsch PM 100 planetary ball-mill.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153068.

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