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Introduction

Nucleophilic aromatic substitution (S_NAr) has played an important role in organic synthesis for a long time.^{1,2} Indeed, the possibility of introducing functional groups on aromatic substrates by replacing a leaving group (often halogen atoms, in particular fluorine) is successfully exploited in pharmaceutical chemistry and in industry,³⁻⁵ thanks to its simplicity, cheapness, and effectiveness, and the absence of traces of metal catalysts in the final products. However, these processes often require high temperature, long reaction time (up to days) and high-boiling polar aprotic solvents, such as dimethylformamide, which are difficult to eliminate and environmentally unfriendly.

In recent years, mechanochemical synthetic methodologies have been constantly gaining importance as a valid alternative to conventional solution processes,6-17 and can address the problem of the use of toxic solvents and high temperature by exploiting mechanical energy furnished by the impacts inside the reactor (jar). In this context, the effectiveness of mechanochemistry applied to S_NAr reactions has been recently demonstrated, providing a substantial advantage in the reaction kinetics compared to the classical procedures in solution.¹⁸ However, a common issue in mechanochemical procedures is the recovery of the crude from the jar. Indeed, especially when organic and inorganic reagents are involved together, a sticky dough remains at the end of the reaction and its recovery requires an huge amount of solvent, compromising the benefits of a solvent-free procedure.18,19 This issue can be addressed using a grinding auxiliary, i.e., an inert material to be added into the reactor together with the reagents, since this often allows the obtainment of a final solid dispersion that is easy to

Al₂O₃ promoted mechanochemical nucleophilic aromatic substitution[†]

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An auxiliary mediated solventless mechanochemical methodology for the nucleophilic aromatic substitution of aryl fluorides by nitrogen nucleophiles without the aid of any base has been developed. The excellent affinity of Al_2O_3 for hydrogen fluoride is the key for this process. Thanks to the use of Al_2O_3 as a milling auxiliary yields of up to 99% were achieved, and the easily processable crude derived from the milling jar allowed a simple and fast work-up procedure, making this method very attractive.

recover and process.²⁰ Besides, the auxiliary can also be effective in switching the reaction selectivity towards the desired products,^{21,22} affecting also the yields depending on its peculiar features.^{23,24} The main drawbacks of grinding auxiliary addition are the dispersion of mechanical energy and the less close contact among the reactants resulting in worsening the reaction kinetic and yield. For these reasons, the individuation of auxiliaries that are able to promote selected transformations is particularly appealing.

Aiming to develop a grinding auxiliary assisted mechanochemical methodology for the S_NAr of aromatic fluorides, we found impressive differences in reaction outputs depending on the nature of the auxiliary used.

Results and discussion

We selected 4-fluoronitrobenzene 1 and piperidine 2a as a model substrate and model nucleophile to set up the milling auxiliary mediated S_NAr reaction (Table 1), as these reagents have already proved to be effective under the auxiliary free milling conditions.18 The more commonly used grinding auxiliary, *i.e.*, silica (SiO₂), was firstly tested. At a $1:1 \frac{1}{2a}$ ratio results were not good both without and in the presence of K₂CO₃ as a base, affording 3a in only 3% and 4% yields, respectively (Table 1, entries 1 and 2). Yield increased to a still unsatisfactory 24% only using a large excess of 2a (Table 1, entry However, the powdery crudes derived from these preliminary attempts were easily recovered, allowing also an easy and fast purification on a silica pad (Fig. S1 and S2[†]). Indeed, thanks to the significant difference in retention factors of 2a, 3a and 1, respectively, and the absence of by-products, the vacuum-aided dry column chromatography methodology²⁵ with a limited quantity of selected eluent was able to afford pure 3a even if the yields were extremely low, a significant improvement if compared with the hard to process sticky dough observed in the case of the reported auxiliary-free procedure.18

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[†] Electronic supplementary information (ESI) available: Synthetic procedures, characterization of all synthesized compounds and copies of NMR and IR spectra. See DOI: https://doi.org/10.1039/d4mr00039k

Table 1 Optimization of mechanochemical S_NAr between 1-fluoro-4-nitrobenzene 1 and piperidine 2ad



^a Reactions were performed using a 50 mL grinding reactor (ZrO₂) and 4 milling balls (1 cm diameter, ZrO_2) at a shaking frequency of 15 Hz, on 2 mmol of 1, using 5 g of auxiliary and 2 equiv. of base (when employed).

The use of a base in S_NAr reactions is generally considered essential and credited to a strong catalytic effect, even though several reports raise doubts on this belief,^{26,27} and looking to a recent high throughput screening of S_NAr the absence of such a catalytic effect is evident.28 This was confirmed in herein reported preliminary tries. It is our opinion that the role of the base is primary to intercept the HF produced during the S_NAr reaction, which, in turn, can protonate the nucleophile making it unreactive. In fact, the use of two equivalents of nucleophile can provide the same results of base addition,^{29,30} and in particular cases, when the base could interfere with the nonbonding interactions required to achieve the transformation, the use of two equivalents of nucleophile is mandatory.^{31,32}

Keeping in mind the concept of intercepting HF, our attention was drawn to costless materials showing also a good affinity for HF, to be used as milling auxiliaries in our procedures. Widely used metal oxides, *i.e.*, titania (TiO₂) and alumina (Al₂O₃), caught our attention; indeed, both have been reported to have an excellent affinity for HF. In the case of TiO₂ this behaviour is mainly exploited as a functionalization strategy to improve the photoelectric and photocatalytic properties of titania-based devices and materials,³³⁻³⁶ whereas the alumina-fluorine affinity has been studied in catalysis,37-39 in biological systems,40 and in industrial applications to scavenge F⁻ ions.⁴¹ Moreover, hydrogen fluoride adsorption on alumina has been investigated by computational methods by Teng and co-workers in 2011.42

First, TiO₂ was tested with our experimental setup at a $1:1 \frac{1}{2}$ 2a ratio without a base for 60 min of milling, affording 3a in 44% yield (Table 1, entry 4). This result confirmed our suppositions on the HF sequestering ability of titania; under the same conditions with SiO₂ as an auxiliary the yield was only 3% (Table 1, entry 1). Addition of K_2CO_3 as a base increased the yield to 67% (Table 1, entry 6), suggesting a cooperative HF sequestration; thus, TiO₂ showed a good but non-optimal HF sequestering ability.

Next, Al_2O_3 was experimented with at a 1:1 1/2a ratio without a base for 60 min of milling, and under these conditions an astonishing 83% yield of pure 3a was achieved (Table 1, entry 7). Right after, we repeated the experiment in the presence of K₂CO₃ (Table 1, entry 8), and base addition had no improving effect achieving the same 83% yield. This confirmed the optimal Al₂O₃-HF affinity to be exploited in the auxiliary mediated mechanochemical S_NAr. Further optimization, *i.e.*, reduction of milling time to 30 min and a 1:1.25 1/2a ratio, allowed the isolation of 3a with a good yield of 91% (Table 1, entry 10).

With these optimized conditions for the Al₂O₃ mediated mechanochemical S_NAr, we tested the procedure with different amines (2b-l, Table 2). The effect of milling time was reevaluated with morpholine 2b (Table 2, entries 1, 2 and 3), and 60 min was found to be the best option since a longer reaction time resulted in a slight advantage in yield; consequently, this parameter was not modified in the subsequent experiments. Increasing the excess of 2b had a more positive impact on the 3b isolated yield, going from 60% to 70% to 96% for 1/2b ratios of 1:1, 1:1.5 and 1:2, respectively (Table 2, entries 3, 4 and 5). The same behaviour was observed for 3pyrrolidinol 2c (Table 2, entries 6 and 7), 4-amino-1-butanol 2h (Table 2, entries 12 and 13) and 2-aminoethanol 2i (Table 2, entries 14 and 15), whereas for the more reactive piperidine 2a a 25% excess was sufficient to exceed 90% yield. The choice for less reactive nucleophiles should be at least a 1:1.5 substrate/ amine ratio. As a matter of fact, an amine excess is a strategy often used in S_NAr methodologies.43

Primary alkylamines were less prone to react with respect to cyclic secondary amines; indeed, 3d was achieved in a modest 32% yield (Table 2, entry 8). Driven by the hypothesis that the lower reactivity was caused by the volatility of butylamine 2d, we experimented with a much heavier alkyl amine, i.e., hexadecylamine 2e, yet the result was significantly worse, and product 3e was isolated in only 3% yield (Table 2, entry 9).

Non-cyclic secondary amines were ineffective; thus, 2f and 2k afforded only barely detectable traces of S_NAr products (Table 2, entries 10 and 17), and N-ethylethanolamine 2j gave 3j in poor 4% yield (Table 2, entry 16).

It is evident that steric hindrance around the nucleophilic site plays a crucial role in S_NAr type reactions; in fact, when hindered primary amine 2g (adamantylamine) was experimented, no traces of expected product 3g were detected (Table 2, entry 11). A particular discussion on this point must be reserved for cyclic amines. Even though they should be more hindered at the nitrogen with respect to linear primary amines, their particular conformation makes the nitrogen lone pair sensibly more prone to carry out a nucleophilic attack; indeed, their nucleophilicity is more pronounced.44,45

In the presence of an OH group on the amine nucleophile (i.e., 2c and 2h-k) N- vs. O-selectivity was complete, and no Osubstitution products were observed. It is worth noticing that

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Table 2 Scope of nucleophiles in the Al₂O₃ promoted mechanochemical S_NAr^a

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Entry	Substrate	Nucleophile	1 : Nu	Time (min)	Product	Isolated yield (%)
1	1	2b	1:1	30	3b	55
2	1	2b	1:1	60	3b	60
3	1	2b	1:1	120	3b	62
4	1	2b	1:1.5	60	3b	70
5	1	2b	1:2	60	3b	96
6	1	2 c	1:1	60	3c	48
7	1	2c	1:2	60	3c	80
8	1	2d	1:2	60	3 d	32
9	1	2e	1:1.5	60	3e	3
10	1	2f	1:1.5	60	3f	Traces
11	1	2g	1:1	60	3g	_
12	1	2h	1:1	60	3h	29
13	1	2h	1:2	60	3h	52
14	1	2i	1:1	60	3i	17
15	1	2i	1:2	60	3i	62
16	1	2j	1:2	60	3j	4
17	1	2k	1:1	60	3k	Traces
18	1	21	1:1	60	31	_
19	1b	2a	1:1	60	3a	15
20^b	1b	2a	1:1	60	3a	4

^{*a*} Reactions were performed using a 50 mL grinding reactor (ZrO_2) and 4 milling balls (1 cm diameter, ZrO_2) at a shaking frequency of 15 Hz, on 2 mmol of 1 or 1b, using 5 g of Al_2O_3 . ^{*b*} 2 equiv. of K_2CO_3 were added.

2h and 2i afforded *N*-substitution products 3h and 3i in 52% and 62% yield, respectively (Table 2, entries 13 and 15); hence, their reactivity was unexpectedly much better with respect to butylamine 2d, whose yield was limited to 32% (Table 2, entry 8). Since the nucleophilic reactivity of 2h and 2i is lower than that of 2d,⁴⁴ we hypothesized a non-bonding interaction between OH and Al₂O₃ which somehow favours the S_NAr reaction.⁴⁶ The low nucleophilicity of the aromatic nitrogen makes aniline 2l unreactive; indeed, no traces of (4-nitrophenyl)phenylamine 3l were detected (Table 2, entry 18). Yet, even in solution this kind of reaction is challenging, requiring very long time at high temperature and/or insanely high pressures.^{47,48}

At last, we experimented under the same conditions with 1chloro-4-nitrobenzene **1b** as a substrate with the more reactive amine nucleophile, *i.e.*, piperidine **2a**. However, **3a** was achieved in only 15% yield (Table 2, entry 19), and even in a worse 4% yield upon adding 2 equiv. of base (Table 2, entry 20). Of course, aryl chlorides are far less reactive than aryl fluorides in S_NAr ; accordingly, with a big increase of the milling time improvements could be observed, but long reaction times in mechanochemical procedures are not convenient; furthermore, it is reported that Cl⁻ adsorption on Al₂O₃ is much less effective compared to that of F^- ;⁴⁹ thus, we decided to not further investigate aryl chlorides with our methodology.

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In order to explore the generality of the method, we used 2fluoropyrazine **4** as a substrate employing the more efficient amine nucleophiles from previous experiments (Table 3). In this case too, the best results were achieved with cyclic secondary amines, *i.e.*, piperidine **2a**, morpholine **2b** and 3pyrrolidinol **2c**; thus, we prepared pure **5a**, **5b**, and **5c** in good yields of 84, 69 and 86%, respectively (Table 3, entries 2, 4 and 5). Good results were obtained also in the synthesis of **5h** from 4-amino-1-butanol **2h** and **5i** from 2-aminoethanol **2i** with a 63 and 61% isolated yield, respectively (Table 3, entries 7 and 8). Conversely, reaction with butylamine **2d** afforded only barely detectable traces of expected product **5d**. *N- versus O*-selectivity was complete even in these cases, and we did not observe any presence of *O*-substituted products.

Next, we tested our methodology with a selection of commercially available fluoroaryl and fluoroheteroaryl substrates in the reaction with piperidine 2a (Scheme 1). First, the effect of the nitro group position in fluoronitrobenzenes was investigated. It is well known that the electronic effect of the activating group in ortho and *para* positions with respect to the leaving group is far more pronounced than the steric effect in S_NAr reactions;¹ indeed, 1-(2nitrophenyl)piperidine 6a was achieved in an excellent 98% yield; conversely, no traces of 1-(3-nitrophenyl)piperidine 7a were detected when 1-fluoro-3-nitrobenzene 7 was reacted under the same conditions. Subsequently, different substituted p-fluoronitrobenzenes (8-12, Scheme 1) were experimented with. Methyl substituted 8a was obtained in 95% yield, and the presence of an additional electron-withdrawing group, *i.e.*, CF₃ in 9 and CN in 10, allowed us to achieve 9a and the key intermediate for the synthesis of antimalarial and antibacterial antimetabolites 10a,50 in almost quantitative yields. Noteworthily, the presence of an NH₂ group on substrate 11 did not prevent the preparation of compound 11a with a good isolated yield of 87%. The latter is a useful intermediate for the synthesis of ferroptosis inhibitors,⁵¹ AMP-activated protein kinase activators,52 fibroblast growth factor receptor

Table 3 Mechanochemical S_NAr between 2-fluoropyrazine 4 and nucleophiles^{*a*}

_ N _ F	2a-i	
Ľ N	Al ₂ O ₃ milling 15 Hz	^ℓ N
4	1 h	5a-i

Entry	Nucleophile	4 : Nu	Product	Isolated yield (%)
1	2a	1:1	5a	73
2	2a	1:1.25	5a	84
3	2b	1:1.5	5b	55
4	2b	1:2	5b	69
5	2c	1:2	5c	86
6	2d	1:2	5d	Traces
7	2h	1:2	5h	63
8	2i	1:2	5i	61

^{*a*} Reactions were performed using a 50 mL grinding reactor (ZrO_2) and 4 milling balls (1 cm diameter, ZrO_2) at a shaking frequency of 15 Hz for 1 h, on 2 mmol of 4, using 5 g of Al₂O₃ as an auxiliary.



Scheme 1 Scope of substrates in the Al_2O_3 promoted mechanochemical S_NAr . Reagents and conditions: substrate (2 mmol), piperidine (3 mmol), Al_2O_3 (5 g), milling (15 Hz), 1 h. ^a 8 g of Al_2O_3 were used to avoid dough formation. ^b Determined by ¹H NMR.

inhibitors,⁵³ and antitumor agents.^{54,55} Substrate **12** was recovered unreacted from the milling attempt due to the high steric hindrance caused by the two methyl groups *ortho* to fluorine.

At this point, we experimented with fluorobenzenes bearing less powerful activating groups, *i.e.*, CN and SO_2Me (13–19,

Scheme 1).1 By reacting 4-fluorobenzonitrile 13 under our conditions 4-(1-piperidinyl)benzonitrile 13a was isolated in a modest 38%. However, the presence of an electron-withdrawing group ortho to the CN sensibly improved the outcome of the milling reaction; indeed, 14a and 15a were achieved in 99% and 89% isolated yield, respectively. It is worth noting that the quantitative yield obtained for the pharmacologically significant nonsteroidal androgen receptor antagonist 14a⁵⁶ outperformed the yields reported to date in the literature, which were limited to 75%.56,57 As expected, when the CN activating groups are placed meta to the leaving fluorine the S_NAr reaction was unfruitful, and no traces of product 16a were detected, while a useless 11% yield of 17a was identified by ¹H NMR analysis of the eluted residue. When 1-fluoro-4-(methylsulfonyl)benzene 18 was employed the S_NAr product 18a was not observed, while the simultaneous presence of SO₂Me and NO₂ groups in the activating positions enabled the synthesis of 19a in an excellent 96% isolated yield.

Finally, pyrimidinyl and pyridazyl fluorides were investigated. Pyrimidine substrates 20 and 21 in which the leaving fluorine is located in the favourable position 2 were successfully transformed into piperidine substituted 20a (an effective antioxidant for the coadjutant treatment of neurodegenerative diseases)58 and 21a with an excellent isolated yield of 95% and 99%, respectively. Pyrimidine compounds which bear the fluorine in the less favourable position 5 are not expected to react in S_NAr, nevertheless, the presence of the CN activating group in the right position in 22 allowed the isolation of pure 22a in 89% yield. 3,6-Diaminopyridazines are key intermediates for the production of pharmaceutically important compounds;59 thus, 6-fluoro-3-pyridazinamine 23 was tested; however, ¹H NMR analysis revealed a poor 9% yield of 23a. It is worth underlining that the powdery crude residues from all experiments were recovered and processed really easily, allowing the isolation of the desired product in pure form in a short time.

To prove the scalability of our methodology we tried a reaction with 10 mmol of aryl substrate. Obviously to maintain the same level of mechanical energy a jar with greater volume should be used, as increasing the quantity of the reagent and auxiliary results in muffling the impacts, and therefore the reaction output could be worse. Nevertheless, **6** (10 mmol), **2a** (15 mmol) and Al_2O_3 (15 g) were charged in a 50 mL reactor (ZrO₂) with 4 milling balls (1 cm diameter, ZrO₂), and the mixture was shaken at 15 Hz for 1 h. After the usual fast purification by vacuum-aided chromatography on silica gel product **6a** was achieved in pure form in a good yield of 91% (Fig. S3†).

Experimental

The detailed synthetic procedures, the characterization of all synthesized compounds and copies of NMR and IR spectra are available in the ESI. \dagger

Conclusions

In summary, we have described a new simple and convenient solventless mechanochemical procedure for the nucleophilic aromatic substitution of aryl fluorides. The HF scavenging View Article Online

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Conflicts of interest

There are no conflicts to declare.

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