RSC Mechanochemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Mechanochem.*, 2024, **1**, 342

Received 21st April 2024
Accepted 8th May 2024

DOI: 10.1039/d4mr00039k

rsc.li/RSCMechanochem

Al_2O_3 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.

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 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 (SiO_2), was firstly tested. At a 1 : 1 **1**/**2a** ratio results were not good both without and in the presence of K_2CO_3 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 4). 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 methodology[25] 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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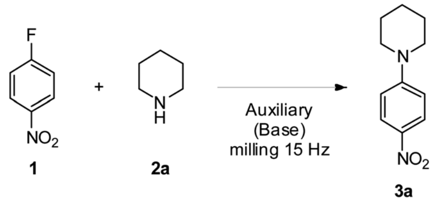
† Electronic supplementary information (ESI) available: Synthetic procedures, characterization of all synthesized compounds and copies of NMR and IR spectra. See DOI: **https://doi.org/10.1039/d4mr00039k**

Table 1 Optimization of mechanochemical S_NAr between 1-fluoro-4-nitrobenzene **1** and piperidine **2a**[a]



1 **2a** **3a**

Entry	**1** : **2a**	Auxiliary	Base	Time (min)	**3a** Isolated yield (%)
1	1 : 1	SiO_2	—	60	3
2	1 : 1	SiO_2	K_2CO_3	60	4
3	1 : 1.5	SiO_2	K_2CO_3	60	5
4	1 : 5	SiO_2	—	60	24
5	1 : 1	TiO_2	—	60	44
6	1 : 1	TiO_2	K_2CO_3	60	67
7	1 : 1	Al_2O_3	—	60	83
8	1 : 1	Al_2O_3	K_2CO_3	60	83
9	1 : 1	Al_2O_3	—	30	88
10	1 : 1.25	Al_2O_3	—	30	91

[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**, 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 non-bonding 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 (TiO_2) and alumina (Al_2O_3), caught our attention; indeed, both have been reported to have an excellent affinity for HF. In the case of TiO_2 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, TiO_2 was tested with our experimental setup at a 1 : 1 **1**/**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 SiO_2 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, TiO_2 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 K_2CO_3 (Table 1, entry 8), and base addition had no improving effect achieving the same 83% yield. This confirmed the optimal Al_2O_3–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 Al_2O_3 mediated mechanochemical S_NAr, we tested the procedure with different amines (**2b–l**, Table 2). The effect of milling time was re-evaluated 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 3-pyrrolidinol **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]

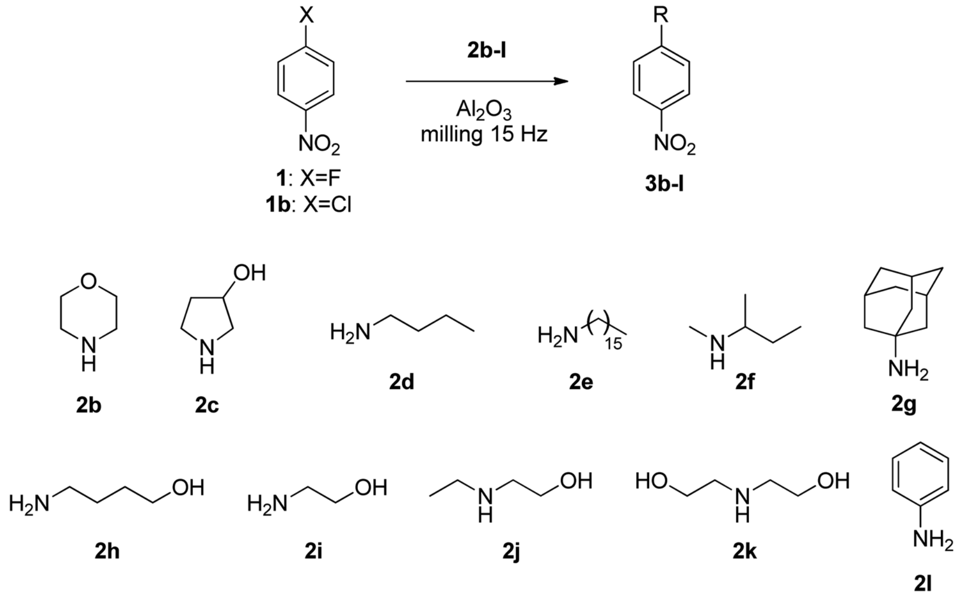
Primary alkylamines were less prone to react with respect to cyclic secondary amines; indeed, **3d** was achieved in a modest 32% yield (Table 2, entry 8). Driven by the hypothesis that the lower reactivity was caused by the volatility of butylamine **2d**, we experimented with a much heavier alkyl amine, *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 *O*-substitution products were observed. It is worth noticing that

Table 2 Scope of nucleophiles in the Al_2O_3 promoted mechanochemical S_NAr[a]



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**	**2c**	1 : 1	60	**3c**	48
7	**1**	**2c**	1 : 2	60	**3c**	80
8	**1**	**2d**	1 : 2	60	**3d**	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**	**2l**	1 : 1	60	**3l**	—
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.

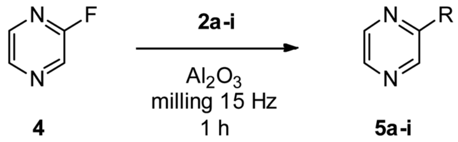
2h and **2i** afforded *N*-substitution products **3h** and **3i** in 52% and 62% yield, respectively (Table 2, entries 13 and 15); hence, their reactivity was unexpectedly much better with respect to butylamine **2d**, whose yield was limited to 32% (Table 2, entry 8). Since the nucleophilic reactivity of **2h** and **2i** is lower than that of **2d**,[44] we hypothesized a non-bonding interaction between OH and Al_2O_3 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 1-chloro-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 Al_2O_3 is much less effective compared to that of F^-;[49] thus, we decided to not further investigate aryl chlorides with our methodology.

In order to explore the generality of the method, we used 2-fluoropyrazine **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 3-pyrrolidinol **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.

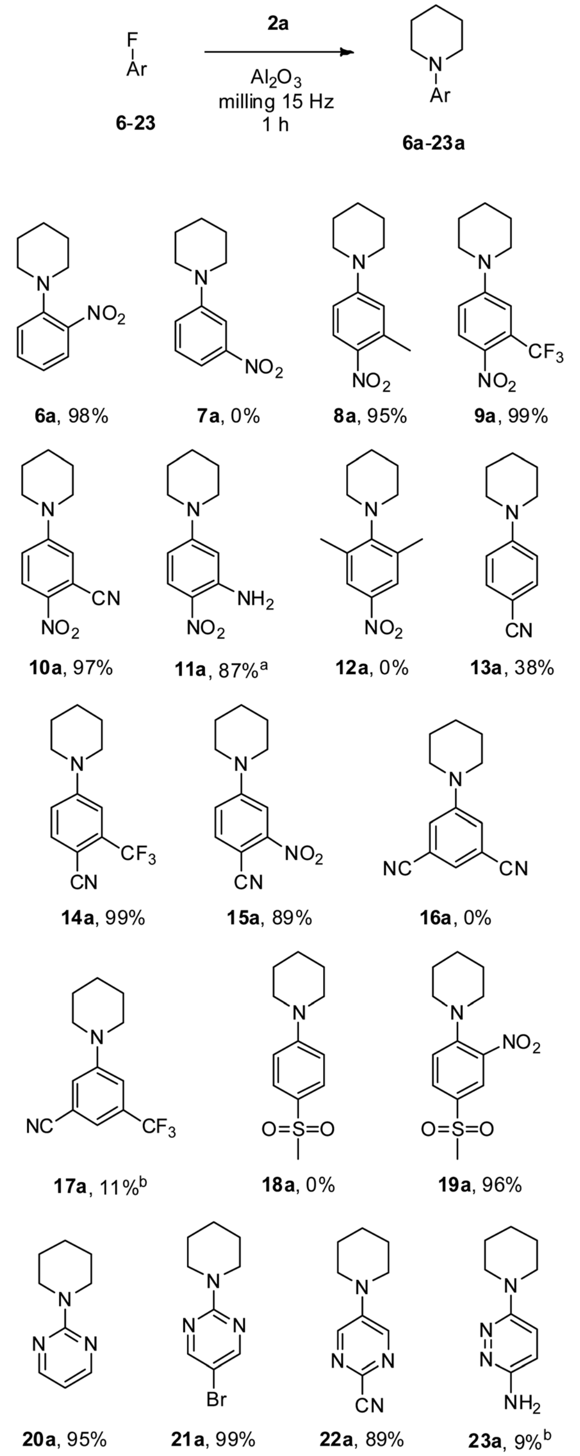
Next, we tested our methodology with a selection of commercially available fluoroaryl and fluoroheteroaryl substrates in the reaction with piperidine **2a** (Scheme 1). First, the effect of the nitro group position in fluoronitrobenzenes was investigated. It is well known that the electronic effect of 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-(2-nitrophenyl)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.*, CF_3 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 NH_2 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 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.

Table 3 Mechanochemical S_NAr between 2-fluoropyrazine **4** and nucleophiles[a]



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 Al_2O_3 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.

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 **14a**[56] 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 SO_2Me and NO_2 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 (ZrO_2) with 4 milling balls (1 cm diameter, ZrO_2), 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.†

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 properties of Al_2O_3 were the key factor, allowing the use of any base to be avoided. Using it as grinding auxiliary facilitated an easy and fast preparation of several amino substituted aryls and heteroaryls in good yields, greatly decreasing the quantity of organic solvent in the work-up step and avoiding the production of aqueous waste that is costly to treat. Cyclic secondary amines and properly activated substrates gave the best results, as expected for this kind of transformation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to thank Giorgio Patriarca for the NMR analyses and Sara Peverali for the photo support.

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