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Under solventfree mechanochemical conditions, treatment of Kobayashi's *o*-trimethylsilylphenyl triflate with tetrabutyl-ammonium fluoride hydrate (TBAF·H₂O) generates benzyne, which reacts with amines to give *N*-phenylated products.

Benzyne formations and reactions with amines under solvent-free conditions in a mixer mill

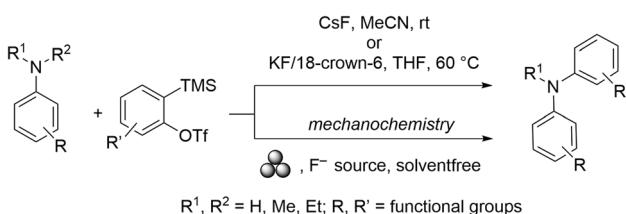
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and coworkers described that analogous transformations were possible by starting from aromatic *tert*-amines (Scheme 1).⁴ In both protocols, Kobayashi's *o*-silylaryl triflates served as precursors of the arynes,⁶ which were generated by addition of either CsF or a combination of KF and 18-crown-6. In those reactions, MeCN and THF were the respective solvents,^{3,4} leading to product formation at room temperature and 60 °C, respectively.

In 2019, IUPAC identified mechanochemistry as an emerging technology that increased sustainability in chemistry.⁷ Since then, its impact in organic synthesis and related areas has widely been documented.⁸ We now wondered if a mechanochemical approach could also improve the environmental footprint in generating arynes⁹ and using them in *N*-arylations of amines. To our delight, we found a first report on such transformations in the web.¹⁰ In 2020, Victor Hellgren had performed a “degree project C in chemistry” under the supervision of Lukasz Pilarski and Matic Hriberek at Uppsala University, and the resulting thesis was published on-line. Various aryne precursors were activated with a mixture of 5 equiv. of CsF and 3 equiv. of 18-crown-6 and the subsequent transformations with potential reactants (including *p*-toluidine as single amino nucleophile) were studied under various mechanochemical conditions using a shaker mill. The depicted (mostly) crude NMR spectra suggested positive reaction outcomes (after 1 h at 36 Hz). Seeing opportunities to improve mechanochemical amine *N*-arylation *via* arynes described by Hellgren, we decided to re-investigate the approach.

Introduction

Aryl amines are key structural units in essentially all organic matter including natural products, pharmaceutical and crop protect agents, materials, and building blocks for synthesis.¹ Consequently, a wide range of methods for their preparation has been devised with numerous examples of reductive and cross-coupling processes.² In most of these amine syntheses, metals are essential as reactants or catalysts, and the reaction conditions are harsh. In contrast, *N*-arylations with arynes are transition-metal-free often proceeding at ambient temperature.^{3–5} For example, in seminal work, Liu and Larock demonstrated that primary and secondary amines reacted with *in situ* generated arynes to provide the corresponding mono- and diarylated products in high yields (Scheme 1).³ Later, Biju



Scheme 1 Known protocols of *N*-arylations *via* arynes (top),^{3,4} this work (bottom).

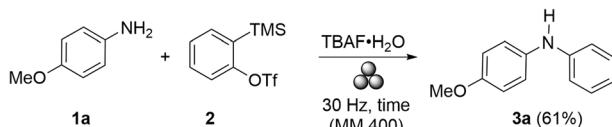
Results and discussion

In the initial phase of our study, we chose *p*-methoxy aniline (**1a**) and *o*-trimethylsilylphenyl triflate (**2**) as representative starting materials (Scheme 2). The reactions were performed in a mixer mill (MM 400) with a stainless-steel (SS) jar and one ball of the same material. While in the first experiments a combination of KF and 18-crown-6 was used as fluoride source (to give **3a** in 62% yield), we pleasingly found that this mixture could be

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Scheme 2 Test reaction for optimising the mechanochemical conditions.

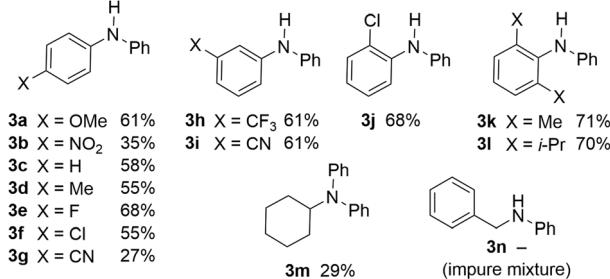
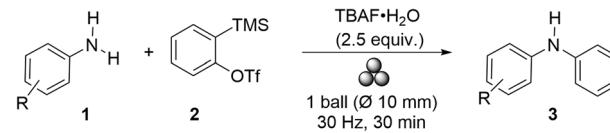
substituted by simple tetrabutylammonium fluoride hydrate (TBAF·H₂O). Thus, with 2.5 equiv. of TBAF and a 1.3-fold excess of 2 (with respect to 1a), the yield of 3a was 61% after 90 min of milling with 1 ball (φ 10 mm) at 30 Hz followed by work-up and isolation of the product by column chromatography. The attempt to use tetramethylammonium fluoride tetrahydrate remained unsuccessful. Shortening of the reaction time from 90 min to 30 min led to full conversion as well. The same result was observed after 30 min when the single ball (φ 10 mm) was substituted by 5 balls (φ 5 mm). In studies with KF and 18-crown-6 a change of the MM 400 to a planetary mill (PM 300) resulted in no significant change in the reaction outcome.¹¹ This was also true, when LAG conditions with acetonitrile and TBAF were applied (in the MM 400).¹²

Performing the reaction (in the MM 400) under the optimised conditions with *p*-nitro aniline (1b) instead of 1a and using a combination of 1.3 equiv. of 2 and 3.0 equiv. of TBAF·H₂O gave diarylamine 3b in 35% yield (Scheme 3).

Reducing the amount of TBAF·H₂O to only 2.0 equiv. had almost no effect, and 3b was isolated in 32% yield. With 2.5 equiv. of TBAF·H₂O and using 3 balls of φ 7 mm instead of 1 ball of φ 10 mm gave 3b in 28% yield. Milling of *p*-nitro aniline (1b) with 1.3 equiv. of 2 and 2.5 equiv. of TBAF·H₂O in a jar made of tungsten-carbide (WC) instead of SS and using a single WC ball (φ 10 mm) afforded 3b in 27% yield.

The aforementioned results led us hypothesizing that electron-donating substituents on the aniline – as represented by *p*-OMe in 1a – had a positive effect on the reaction outcome, whereas electron-withdrawing groups (such as *p*-NO₂ in 1b) hampered the *N*-arylation. This view was largely supported by the subsequent results (Scheme 4).

In general, the yields for products stemming from anilines were in the 55–70% range. The only exceptions were, as expected, *p*-nitro- and *p*-cyano-substituted compounds 3b and 3g which were obtained in only 35% and 27%, respectively. The highest yield among *para*-substituted anilines was observed for 3e bearing a *p*-fluoro substituent (68%). Products 3h and 3i with *meta*-CF₃ and -CN groups were both obtained in 61% yield. To our surprise, anilines with *ortho*-substituents (1j–l) reacted very

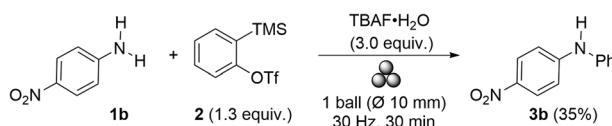


Scheme 4 Substrate scope of the mechanochemical *N*-phenylation.

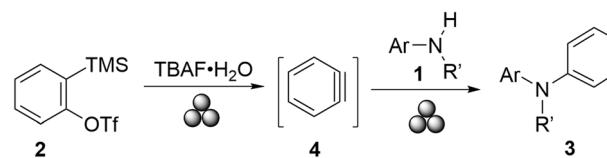
well providing the corresponding products in yields of 68%, 70%, and 71%, respectively. More in depth studies with *ortho*-chloro-substituted aniline 1j showed that the use of 3 balls of φ 7 mm (instead of 1 ball of φ 10 mm) had only a minor effect on the yield of 3j (60% *versus* 68%). Switching to the WC equipment as before gave 3j in 60% yield. Reactions of non-aromatic amines were of low productivity as revealed by the data for (cyclohexyl)diphenylamine (3m) which was obtained by double phenylation of cyclohexylamine in only 29% yield and benzyl-phenylamine (3n) being part of a non-separable product mixture. It is well possible that the phenylation of 1m provided some of the mono-*N*-phenylated (or over-*N*-arylated) product as well, but under the standard work-up conditions it remained undetected.

In terms of the mechanism, we believe to be in line with former proposals (Scheme 5).^{3–5}

Benzyne (4) is generated from *o*-trimethylsilylphenyl triflate (2) by activation with fluoride. Remarkably, under these solventfree mechanochemical conditions, simple tetrabutylammonium fluoride hydrate can be used as fluoride source thereby avoiding more expensive and complex reagent combinations (such as CsF or KF/18-crown-6). Subsequent amine-to-benzyne additions provide the *N*-phenylated products 3. Of note is that the generated byproducts (including TMS-F or their hydrolysed counterparts as well as TBAOTf) do not seem to interfere the product formation. The same is true for the possible di- or trimerisation reactions of 4, which appear to play a minor role only (if any). Products of such reactions have neither been observed nor isolated.



Scheme 3 *N*-Arylation of 1b with 2 and TBAF under the optimised conditions.



Scheme 5 Mechanistic proposal for the *N*-arylation.



Conclusions

In summary, we investigated mechanochemical *N*-phenylations of amines proceeding *via* benzyne. The aryne precursor (*o*-trimethylsilylphenyl triflate) is readily available, and can easily be activated by tetrabutylammonium fluoride hydrate. Under solventfree conditions, the *in situ* generated benzyne then reacts with amines to give their *N*-phenylated counterparts.

Author contributions

G. R. and D. R. carried out the experiments and data analysis. C. B. conceptualised, supervised, and administrated the project. He also wrote the initial draft of the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

G. V. R. and D. R. are employed by PI Industries Ltd.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details, NMR spectra and data. See DOI: <https://doi.org/10.1039/d5mr00109a>.

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11 Milling of 2.5 equiv. of KF in combination with 2.5 equiv. of 18-crown-6 in a PM 300 ball mill equipped with a SS jar (12 mL) and two SS balls (10 mm) at 700 rpm for 90 min gave **3a** in 65% yield. Using TBAF under similar conditions, provided **3a** in a yield of 64%.

12 The attempt to use LAG with MeCN and a combination of KF and 18-crown-6 in the PM 300 led to **3a** in 40% yield.

