

Investigation of Mechanochemical Thianthrene-Mediated Aryl C–H Functionalization

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Abstract: We report an efficient solvent-free approach for palladium-catalyzed coupling reactions exploiting *S*-aryl-thianthrenium salts as intermediates. All reaction steps – thianthrene oxidation, arene thianthrenation, and thianthrenium salt functionalization – can be achieved with high yields mechanochemically, without the need for inert conditions, thus offering significant savings in time, energy, and organic solvents.

Keywords: thianthrene, arene C-H functionalization, mechanochemistry, solid-state synthesis, ball milling.

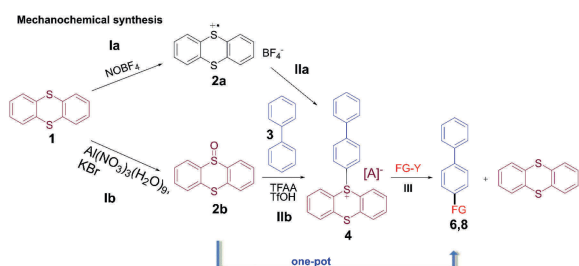
INTRODUCTION

THIANTHRENE (**1**) has long been known for its susceptibility to oxidation and transformation induced by the action of sulfuric acid, resulting in the formation of a distinctive red-coloured radical cation.^[1] As far back as 1965, Shine and co-workers made pioneering contributions to thianthrene chemistry by successfully synthesizing and identifying aryl thianthrenium salts.^[2,3] This was realized through treatment of thianthrene cationic radical with aliphatic and aromatic substrates in strongly acidic conditions, setting a significant milestone in the exploration of thianthrene's applications in synthesis.^[4]

In the past few years, aryl thianthrenium salts have been recognized as useful intermediates and applied extensively for the development of new protocols for coupling reactions, in particular for various aryl C-H functionalization reactions.^[5,6] Thianthrenation can proceed both on electron-rich and electron-poor aromatics, whereby the reactivity and thus reaction efficiency can be tuned by *e.g.* using fluorinated thianthrene derivative, as well as by choosing between several acids and/or anhydrides.^[5,7] Thianthrenium radical cations are highly regioselective and react with aromatics exclusively at the *para*-position. In the

synthesis of thianthrenium salts, different types of acids, such as perchloric acid and acetic anhydride along with inorganic (AlCl₃), or organometallic reagents have commonly been employed. However, these methods often resulted in moisture and air-sensitive products.^[4,8,9] New protocols for synthesis of aryl thianthrenium salts, developed by Ritter and his co-workers, typically involve thianthrene-*S*-oxide (**2b**) or more reactive tetrafluorothianthrene-*S*-oxide, both in the presence of an anhydride and strong acids such as triflic acid (TfOH), trifluoroacetic acid (TFA) or tetrafluoroboric acid diethyl ether complex (HBF₄OEt₂), followed by base workup and anion exchange, finally yielding air-stable products.^[5] Using an anhydride is of particular relevance, as it enables a very effective reaction pathway involving acylated intermediates.^[5,10] Although this method offers high reactivity of prepared salt and tolerates various functional groups during the reaction, it often requires inert conditions, dry solvents, and cooling much below room temperature. Despite these challenges, conceptual advantages such as versatility and regioselectivity with high yields make aryl thianthrenium salts highly valuable intermediates in organic synthesis.

To improve the practicability of the thianthrene-mediated pathways for the functionalization of aryl



Scheme 1. Explored reaction pathways for thianthrene (**1**) oxidation, thianthreination of biphenyl (**3**), and functionalization reactions.

compounds, we explored the application of mechanochemistry, specifically ball milling. In particular, we present a scalable mechanochemical method for the synthesis of **2b** as a precursor for thianthreination reactions, then for preparing aryl thianthrenium salt (**4**), and finally for functionalization reactions (Scheme 1). In our research we opted for the commercially available non-fluorinated thianthrene (**1**). Most importantly, we demonstrate that the sensitive thianthreination reaction can be efficiently performed under ambient atmosphere and room temperature, that the thianthrenium salt isolation step can be simplified or even omitted, and that functionalization reactions can be readily performed by ball milling.

RESULTS AND DISCUSSION

Thianthrene-mediated aryl C-H functionalization can be divided into three main steps: thianthrene (**1**) oxidation (Scheme 1, I), thianthreination (Scheme 1, II), and functionalization (Scheme 1, III). Steps I and II can also be run by first oxidizing **1** into its radical cation (**2a**), and then reacting the radical with the aryl substrate,^[5,11,12] while steps II and III could be combined into a one-pot reaction. Our attempts to produce radical cations by milling, and to produce thianthrenium salts directly by milling nitrosonium tetrafluoroborate (NOBF₄) with **1** and an aryl substrate yielded no detectable amounts of products, while handling thianthrenium radical cation (**2a**) salt in the atmosphere was not possible without its rapid and complete degradation (see SI, Sections 3 and 6.1). Such outcomes match previously noted extreme sensitivity of **2a** to the atmosphere.^[9] While the possibility of a successful reaction in an inert atmosphere cannot be excluded, we decided to focus our efforts on developing procedures suitable for standard ambient conditions.

Thianthrene Oxidation

There are several reported procedures for the oxidation of thioethers into corresponding S-oxides, most with good to excellent yields.^[12–14] In our study, we opted for bromide-

catalyzed oxidation with nitrate in mildly acidic conditions, due to its inexpensive reactants and the ease of operation. We improved this method by transferring it to a ball mill, achieving excellent yields and reduced reaction times (from stirring for 3 h to milling for less than 80 min, see SI, Figure S3). We have also found that the reaction can be efficiently performed on the multigram scale, in a planetary ball mill, with the reaction time of 6 h.^[5]

Biphenyl Thianthreination

Biphenyl (**3**) thianthreination (Scheme 1, IIb) was performed both in solution, following a known literature procedure,^[15] and mechanochemically. As the first step we set to check whether purification of the product can be achieved without column chromatography. To our delight, we found that fine crystalline material can be obtained by dissolving the raw product in a small volume of very cold DCM, and precipitating it by adding cold diethyl ether while vigorously scratching and mixing with a spatula. A similar procedure was mentioned in the literature,^[10] but, as we found, without cooling the product separates as an oil that could not be handled.

Exploration of mechanochemical routes deals with several different aspects. First we explored alternatives to expensive and environmentally unfriendly fluorinated acids and anhydrides, including using reduced amounts thereof. Unfortunately, the results unequivocally show that using triflic acid in combination with trifluoroacetic anhydride gives superior yields in comparison with using sulfuric acid and acetic anhydride (Table 1, entries 1,2). In the same line, using smaller amounts of the acid and the anhydride severely impacts the yields and limits the setup close to the composition in the liquid synthesis (Table S1, entries 5–8). On the other hand, we have found that good yield (73 %) can be obtained mechanochemically, while working at room temperature and in contact with the atmosphere has only a limited effect on the reaction in the mechanochemical setting.

Table 1. Optimization of reaction conditions for thianthreination of **3**.^(a)

Entry	Acid	Anhydride	Additive	Yield / % ^(b)
1	TfOH (2 eq.)	TFAA (3 eq.)	-	73
2	H ₂ SO ₄ (1 eq.)	Ac ₂ O (3 eq.)	-	5.2
3	TfOH (2 eq.)	TFAA (3 eq.)	NaOTf (500 mg)	86
4 ^(c)	TfOH (2 eq.)	TFAA (3 eq.)	Na ₂ SO ₄ (300 mg)	49
5 ^(c)	TfOH (2 eq.)	TFAA (3 eq.)	NaBF ₄ (300 mg)	47

^(a) Reaction setup: mixer mill, 30 Hz, 14 mL teflon jar, ZrO₂ milling balls (2 × 1.6 g), 120 min, air, r.t., **2b** (0.43 mmol), **3** (1 equiv.).

^(b) NMR yield determined using an internal standard.

^(c) PMMA jar.

Due to the high amount of acid and anhydride (both liquids) added relative to the solids, the resulting reaction mixtures were in the form of oils or slurries. Besides, we noticed that poly(methyl-methacrylate) (PMMA) jars were partly dissolving in the reaction mixtures. Therefore, aside from replacing PMMA with Teflon in later experiments, we also set out to explore solid additives, in order to improve mechanical properties of the reaction mixtures. For that purpose, we employed some commonly-used additives, such as silica, alumina, or NaCl, as well as some that are less common, such as sodium tetrafluoroborate and sodium triflate. Much to our surprise, adding silica, alumina, NaCl, or TiO₂ were detrimental and led to extremely low yields (Table S2, entries 7–11), while sodium sulphate and sodium tetrafluoroborate gave moderate yields (Table 1, entries 4, 5). Altogether, only sodium triflate, and only in combination with 2 equivalents of TFOH and 3 equivalents of TFAA, led to a high yield of 86 % (Table 1, entry 3).

Thianthrenyl-Biphenyl Functionalizations

The aryl thianthrenium salt (**4**), formed in the reaction of **2b** and **3** (Scheme 1), was further tested as an aryl electrophile to form new C-C and C-N bonds. First we investigated the Suzuki-Miyaura reaction of **4** with phenylboronic acid (**5a**) and 3-thiopheneboronic acid (**5b**) in the presence of palladium catalyst and a base, at room temperature, both by NG (eng. *neat grinding*) and by LAG (eng. *liquid-assisted grinding*) (Scheme 2). Reaction setup was designed similarly to procedures used for previously reported mechanochemical Suzuki-Miyaura reactions.^[16–19]

We tested three palladium catalysts: Pd(OAc)₂, Pd(PPh₃)₄, and PdCl₂. Pd(PPh₃)₄ was the most efficient catalyst (Table 2, entries 1 and 4). Further optimization of the reaction was done with **5a** and the less expensive and air-stable Pd(OAc)₂, despite its lower yield. Using KHCO₃ or K₃PO₄ × H₂O instead of K₂CO₃ decreased the yields (Table S3). Varying the amount of the base showed that the yield could be improved by adding 4.0 instead of 2.4 equivalents of base, while other amounts of the base reduced the yield (Table 2, entry 7, see also Table S3). Adding *i*-PrOH as a liquid additive significantly reduced the yield (Table 2, entry 8). Most likely the reason was mechanical, since the reaction mixture turned into a semi-solid mass stuck to the balls



Scheme 2. Mechanochemical Suzuki-Miyaura C-C coupling reaction.

and the jar walls. Other liquids were not tested further. Decreasing the amount of **5a** to 1.1 or 1.2 equivalents (Table S3) did not improve yield, and a similar outcome was found when a solid additive was used (NaCl, Table 2, entry 9). Reducing the amount of catalyst, while proportionately increasing the reaction time, significantly reduced the yield (Table S3). Reaction kinetics was monitored by *ex situ* ¹H NMR spectroscopy (Table S4) and it was found that 3 h reaction time is optimal.

One-pot mechanochemistry offers significant advantages over reported solution-based approaches that consume time, energy and materials, so we tested its feasibility for the thianthrene-mediated functionalizations. Taking all the ingredients for both steps of thianthrenation and the subsequent Suzuki-Miyaura reaction could not lead to any products since the acid, anhydride and the base in large excess would react immediately, thus precluding the formation of the thianthrenium salt. To mitigate the acid-base neutralization we tried a single-step one-pot reaction without the acid. Unfortunately, we detected only traces of product (Table 2, entry 10). However, when the thianthrenation step was followed by adding the materials

Table 2. Optimization of reaction conditions for mechanochemical Suzuki-Miyaura reaction.^(a)

Entry	R-B(OH) ₂	Catalyst	Yield / % ^(b)
1	5a	Pd(PPh ₃) ₄	90
2	5a	Pd(Cl) ₂	74
3	5a	Pd(OAc) ₂	72
4	5b	Pd(PPh ₃) ₄	63
5	5b	Pd(OAc) ₂	54
6	5b	Pd(Cl) ₂	28
7 ^(c)	5a	Pd(OAc) ₂	84
8 ^(d)	5a	Pd(OAc) ₂	44
9 ^(e)	5a	Pd(OAc) ₂	39
10 ^(f)	5a	Pd(OAc) ₂	Traces
11 ^(g)	5a	Pd(OAc) ₂	53

^(a) Reaction setup: mixer mill, 30 Hz, 7 mL PMMA jar, one ZrO₂ milling ball (1.6 g), 3 h, air, r.t., **4** (0.1 mmol), **5a-b** (1.3 equiv.), Pd catalyst (5 mol%), K₂CO₃ (2.4 equiv.).

^(b) NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard.

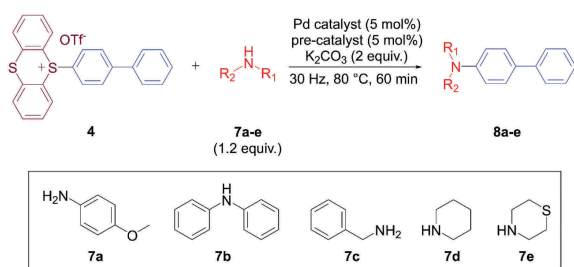
^(c) 4 equiv. K₂CO₃ added.

^(d) *i*-PrOH (10 μL) added.

^(e) NaCl (100 mg) added.

^(f) One-step one-pot reaction: 14 mL teflon jar, two ZrO₂ milling balls (1.6 g), 3 h, air, r.t., **2b** (0.43 mmol), **3** (1 equiv.), TFAA (3 equiv.), **5a** (1.3 equiv.), K₂CO₃ (6.4 equiv.), and Pd(OAc)₂ (5 mol%).

^(g) Two step one-pot reaction: 14 mL teflon jar, two ZrO₂ milling balls (1.6 g). 1st step: 3 h, air, r.t., milling of **2b** (0.43 mmol), **3** (1 equiv.), TFOH (2 equiv.), TFAA (3 equiv.), 2nd step: in the same jar, milling for 3 h after addition of **5a** (1.3 equiv.), K₂CO₃ (6.4 equiv.), and Pd(OAc)₂ (5 mol%).



Scheme 3. Mechanochemical Buchwald-Hartwig C–N coupling reaction.

for the Suzuki-Miyaura reaction, without isolating the thianthrenated salt, a good yield of 53 % was obtained (Table 2, entry 11).

Secondly, we examined the Buchwald-Hartwig reaction, in particular by reacting the **4** with several primary and secondary aromatic and aliphatic amines (**7a–e**) (Scheme 3). Inspired by work of Lemesre *et al.*, we applied the catalytic system Pd(OAc)₂ in combination with tBuXPhosPdG3.^[22] It exhibited high efficiency with *p*-anisidine (**7a**) (94 %, Table 3, entry 1), while, unfortunately, significantly lower yields were observed with secondary aliphatic amines thiomorpholine (**7e**) and piperidine (**7d**), as well as with diphenylamine (**7b**) and benzylamine (**7c**) (Table 3, entries 2–5). Changing the base, temperature, (amounts of) catalysts etc. systematically led to drastic decrease of yields for **7a** (SI, Table S5).

CONCLUSIONS

In summary, we show that the mechanochemical approach represents a viable alternative to solution-based thianthrene-mediated aryl functionalizations. Firstly, preparation of **2b** can be efficiently performed either in a ball mill or at a larger scale in a planetary mill, with excellent reaction time and yields. Furthermore, we have developed mechanochemical route to solid-state aryl thianthrenium salt **4** in ambient conditions without significantly impacting the yield, while purification step can be simplified or even omitted, in the case of one-pot reaction. Especially important for the thianthrenation of **3** was the use of sodium triflate as an additive, since rheology of the reaction mixture was found important for the success of the reaction. Finally, we have found that using thianthrenium salt as a reactant for C–C coupling with aryl boronic acids, as well as C–N coupling, can be performed with satisfactory yields in a mechanochemical setting. In particular, Suzuki reaction, facilitated by Pd catalysts without expensive ligands, was completed within a short time frame, and with yields comparable both to literature reports for mechanochemical^[16–19] and solution approaches.^[20,21] Buchwald-Hartwig amination, on the other hand, has reached near-

quantitative yield for one substrate, although others yielded less, ranging from 7 to 25 %. Such an outcome is however not surprising, as Buchwald-Hartwig reaction often requires harsh conditions and lower yields might be expected.^[23–25] By successfully conducting these reactions at higher temperatures without extending milling duration, we further validated the efficacy of this approach. At present, thianthrene-mediated reactions in mechanochemical environment are scarce compared to its application and exploration in solution. The examples presented here would suggest a potential for further development and may offer superior synthetic pathways for aryl compounds.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: <https://doi.org/10.5562/cca4097>.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from [Adobe's web site](https://www.adobe.com/acrobat).

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