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Reductive Alkylation of Arenes by a Thiol-Based Multicomponent Reaction

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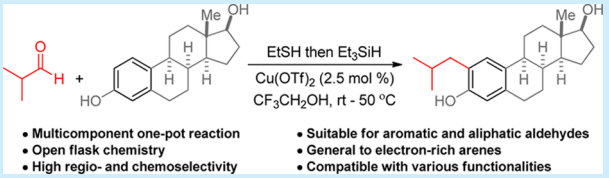
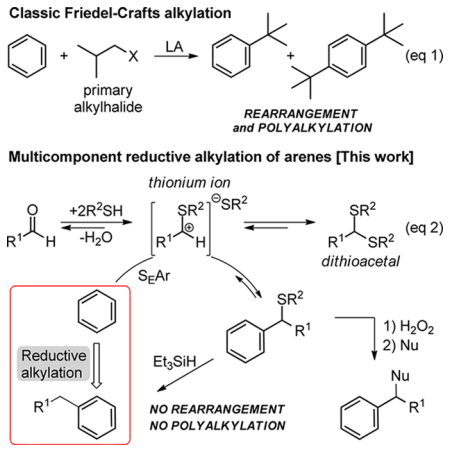
Supporting Information

ABSTRACT: A simple and highly chemo- and regioselective method for introducing primary alkyl substituents into aromatic compounds was developed. The method is based on an electrophilic aromatic substitution of an aldehyde, promoted by a thiol, to afford 1-(alkylthio)alkylarenes, which can either be reduced in situ with triethylsilane or reacted further. This multicomponent reaction enables the direct introduction of both aromatic and linear and branched aliphatic alkyl groups into arenes. The above one-pot protocol may be performed in air and in the presence of water and is compatible with various functional groups.



The introduction of primary alkyl groups into aromatic compounds is one of the oldest synthetic problems that still pose a challenge to chemists today despite the enormous progress that has been made in organic synthesis since the pioneering work of Charles Friedel and James M. Crafts on the substitution of aromatic C−H bonds with alkyl halides in the presence of $AlCl_3$.[1,2] Over the years, the classic Friedel−Crafts reaction has seen a number of improvements, leading to the development of novel techniques that are more selective, nontoxic, and less harmful. Indeed, this reaction has become the method of choice for the introduction of allyl and benzyl groups[3] and secondary and tertiary alkyl moieties.[3] Nonetheless, due to mechanistic constraints, the alkylation of primary alkyl groups requires harsh conditions[4] and is ineffective in that it results in the formation of a mixture of rearrangement products (Scheme 1, eq 1). Other major drawbacks, such as polyalkylation of the aromatic core and a strict requirement for anhydrous conditions, further affect the applicability of the process. To address the synthetic difficulties of attaching primary alkyl groups to aromatic compounds, alternative multistep protocols have been developed, such as Friedel−Crafts acylation and reduction, reductive Friedel−Crafts benzylation and allylation,[5] metal-catalyzed cross-coupling,[6] and metal-catalyzed C−H activation.[7]

Scheme 1. Classic Friedel−Crafts Alkylation (eq 1), Reductive Alkylation of Arenes (eq 2)



Here, we disclose a practical solution to this long-standing synthetic problem (Scheme 1, eq 2) of directly attaching the primary alkyl group to aromatic compounds. The novel transformation is based on the electrophilic aromatic substitution of arenes and heteroarenes by a thionium ion, which is produced in situ from aldehydes and thiols under mild acid-catalyzed conditions. This efficient and highly chemo- and regioselective Pummerer-type reaction affords 1-(alkylthio)alkylarenes, which can either be reduced in situ to the corresponding saturated benzyl or alkylarenes (Scheme 1, eq 2) or, alternatively, used as synthetic intermediates. This multicomponent reaction is suitable for both aromatic and linear and branched aliphatic aldehydes, and it is compatible with a variety of functionalities and reagents including alkyl halides and alcohols, which are the substrates of the classic Friedel−Crafts reaction. Other advantages are that the reaction is water tolerant, does not require corrosive reagents or toxic halides, and can be applied to the direct alkylation of important biologically active compounds.

The chemistry of the thionium ion, also known as the Pummerer reaction, has been applied in numerous transformations and applications.[8,9] Relevant to the current work, the reactivity of aromatic thionium ions toward aromatic π-bonds has been investigated by several groups.[8,9q] In those studies, the powerful electrophile was generated from aromatic sulfoxides,[9q] thioacetals (*connective* Pummerer),[9o] or dithioacetals that were prepared in advance.[9l,m,o] Undesired side processes, e.g., Pummerer rearrangement, were usually prevented by the use

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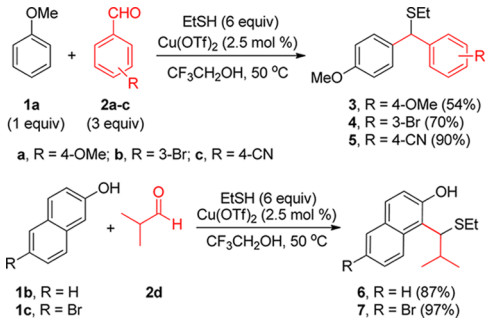
of kinetic conditions that include stoichiometric amounts of activators such as Ac_2O, Tf_2O, TMSOTf, or $SnCl_4$, in moisture-free solvents at reduced temperatures. Under these harsh acidic conditions, only substrates that are unreactive toward acid or acylating reagents are compatible, and as a result of competitive side reactions, the chemistry has mainly been applied for cyclization of small- and medium-sized rings.[9s,10]

Recently, our group has developed an attractive approach, governed by thermodynamic considerations, to transform aldehydes into thionium ion intermediates.[11] We demonstrated, that aldehydes and thiols react under certain conditions [$Cu(OTf)_2$ (5 mol %) in CH_3NO_2 or CF_3CH_2OH] to form dithioacetals that exist in a rapid equilibrium with their thionium ion intermediates (Scheme 1B). In the presence of ketones, a selective cross-addition takes place, producing β-ketosulfides in a single step via a unique mechanistic scheme.[11] Encouraged by these results, we investigated the reactivity of aromatic compounds toward thionium ions under our mild Lewis-acid catalyzed conditions.

We began our investigation by exploring the reactivity of aromatic aldehydes toward anisole in the presence of ethanethiol under a modification of previously reported conditions [$Cu(OTf)_2$ (2.5 mol %) in 2,2,2-trifluoroethanol, 50 °C, Scheme 2].[11] While the substitution of 4-anisaldehyde afforded 1-

Scheme 2. Alkylation of Arenes with Aldehydes by Thiol-Based Multicomponent Reaction



(ethylthio)benzylarene **3** as a single product in moderate yield (54%), the reaction with electron-deficient benzaldehydes (R = Br and R = CN) exhibited higher reactivity, leading to coupling products **4** and **5** in 74% and 90% yields, respectively. Similar to other electrophilic aromatic substitution reactions, this transformation is reversible: the 1-(ethylthio)benzylarenes can revert back to the dithioacetal and the arene coupling partners (see Supporting Information (SI) for further details). This reversibility may explain the high *para*-selectivity that was observed in the above examples. Different thiol-promoters can be used; for example, the benzylation of benzaldehyde with electron-rich arenes produced 1-(alkylthio)benzylarenes **8**−**11** (Figure 1) in moderate to excellent yields. While ethanethiol and isopropylthiol exhibited similar reactivity and required prolonged heating (4−7 h) at 50 °C to reach satisfactory conversions (products **8** and **9**, 94% and 92% yields, respectively), the reaction of benzaldehyde with 2,6-dimethylphenol, using thioacetic acid as the promoter, reached completion within minutes at room temperature, affording product **12** in 98% yield. High chemoselectivity was observed, and polar functional groups, such as −OH (products **11**−**13** and **15**), $-CO_2H$ (**14**), −CN (**16**,**17**), and $-NMe_2$ (**19**), were left untouched under the reaction conditions. Mesitylene (**16**) and thioanisole (**17**) are the least

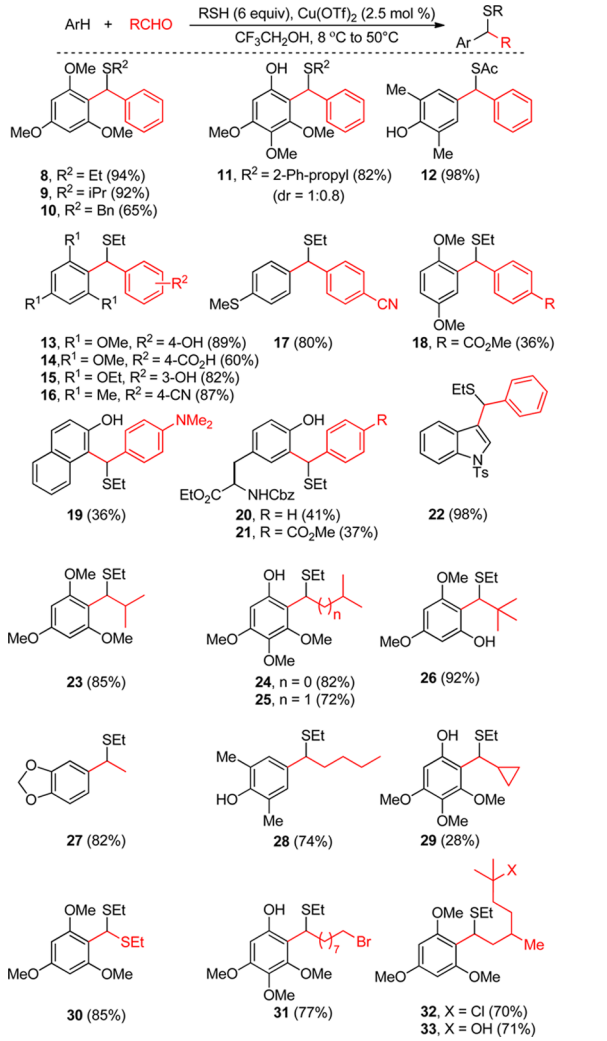


Figure 1. Scope of the thiol-based multicomponent alkylation of arenes. For the exact reaction conditions, see SI.

reactive arenes that we were able to react under the developed conditions. To demonstrate the suitability of the method for complex biologically active compounds, we successfully alkylated *N*-Cbz-protected tyrosine (products **20** and **21** in 41% and 37% yields, respectively) and an *N*-Ts indole (**22**, 98%).

Next, the alkylation of arenes with aliphatic aldehydes was examined. The tendency of enolizable aldehydes to undergo self-coupling under acidic conditions precludes their application in S_EAr reactions. Indeed, the reaction of 2-naphthol (**1b**) with an excess of isobutyraldehyde (**2d**) under our general conditions, in the absence of thiol, produced a complex reaction mixture (see SI). This picture changed completely when the reaction was performed in the presence of ethanethiol (Scheme 2); the aliphatic aldehyde was protected as dithioacetal, which transformed to an active thionium ion species. This ion, in turn, reacted with naphthols **1b** or **1c**, affording benzylsulfides **6** or **7** in excellent isolated yields of 87% and 98%, respectively. Both linear and branched aliphatic aldehydes are suitable reactants for this reaction, including sensitive aldehydes (product **29**), and afforded 1-(ethylthio)alkylarene derivatives **23**−**28** and **30**−**33** in high yields (Figure 1). Side processes, such as rearrangement, polyalkylation of the aromatic ring, or cationic reactions on the benzylsulfide group, were not observed.[10a] The reaction of 1,3,5-trimethoxybenzene (**1d**) with trimethyl orthoformate provided a

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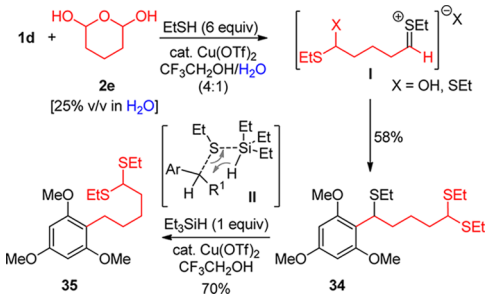
direct entry to masked aldehyde **30** in 85% yield. Notably, primary and tertiary alkyl halides and tertiary alcohols, which are common substrates in the classical Friedel–Crafts reaction, were stable under the mild acidic conditions (products: **31**, 77%; **32**, 70%; **33**, 71%).

Contrary to the classic Friedel–Crafts alkylation, which requires anhydrous conditions, the reversibility of this process endows it with tolerance to water, as exemplified in the coupling of an arene **1d** with glutaraldehyde (**2e**, 25% v/v in H_2O, Scheme 3). This aldehyde is probably transformed into the thionium ion **I** before reacting with the arene to afford the dithioacetal **34** in a moderate 58% yield.

Scheme 3. Electrophilic Aromatic Substitution of Glutaraldehyde in Water



To successfully address the historical problem of direct rearrangement-free alkylation of arenes with primary alkyl groups, it was essential to find a suitable desulfurization agent that would be (1) compatible with the reaction's mild acidic conditions [$Cu(OTf)_2$ (2.5 mol %) in CF_3CH_2OH] and with water residues and protic functionalities, (2) highly chemoselective, and (3) sustainable and economically acceptable. Although many reducing reagents are suitable for conducting this transformation,[12] including SmI_2 that was successfully applied by Procter,[9k−p,12c] triethylsilane (Et_3SiH), which has the ability to deliver hydride ions under acid-catalyzed conditions and meet the above requirements, was examined. Indeed, when compound **34** was treated with Et_3SiH (1.5 equiv) under our general reaction conditions, selective reduction of the benzylic sulfide group took place (without affecting the dithioacetal functionality), affording the desired masked aldehyde **35** in 70% yield (Scheme 3). We speculate that the reduction step involves an intermolecular hydrogen transfer to an ion-pair framework of the activated complex **II** (Scheme 3),[13] which liberates both the reduced product and GC-MS detectable $EtS{-}SiEt_3$.

The compatibility of triethylsilane with our mild acid-catalyzed conditions enables a one-pot reductive alkylation reaction that begins with the substitution of the aldehyde to the arene in the presence of an ethanethiol promoter. Upon completion of the coupling step, as indicated by TLC, the sulfide group is selectively reduced by the addition of Et_3SiH to the reaction mixture. The generality of the protocol was examined, and the results are shown in Figure 2. The method is efficient for introducing linear and branched primary alkyl substituents. Alkyl groups, such as methyl (product **36**, 51% yield), ethyl (**37**, 81%), isobutyl (**38**, 73%; **41**, 87%; **42**, 78%), isopentyl (**40**, 78%), neopentyl (**43**, 70%), and nonanyl (**44**, 62%), were attached to various aromatic compounds in a single synthetic step with high chemo- and regioselectivity. Importantly, functional groups that are incompatible with other alkylation methods and/or are sensitive to reduction, such as tertiary alcohols (**46**, 77%), tertiary

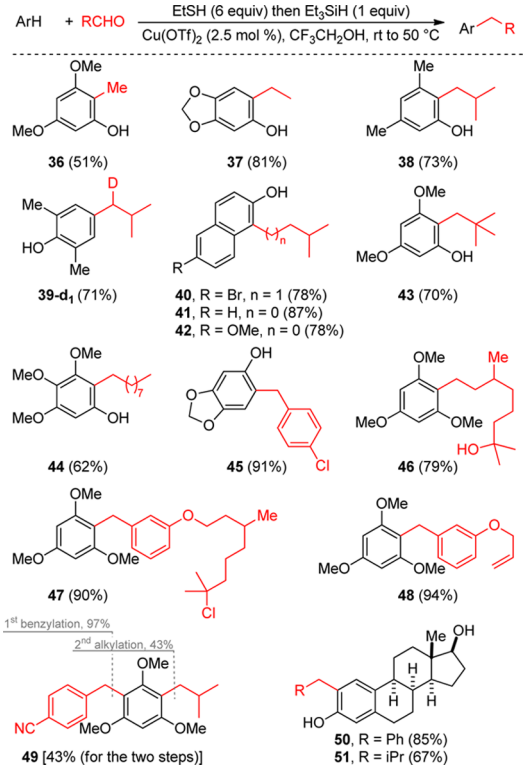


Figure 2. Scope of the reductive alkylation reaction. For the exact reaction conditions, see SI.

alkyl chlorides (**47**, 90%), and alkenes (**48**, 85%), were not affected, thereby offering additional synthetic possibilities. Derivatization of the sex hormone 17β-estradiol was possible with both aromatic (**50**, 85%) and aliphatic (**51**, 67%) aldehydes, offering new opportunities in medicinal chemistry. An isotope-labeled alkyl group was attached by using Et_3SiD as the reducing agent, affording **39-d$_1$** in 71% yield. Finally, this multicomponent reaction can be carried out with improved atom economy,[14] as demonstrated by the alkylation of arene **1d** (1 equiv) with benzaldehyde **2f** (1 equiv) and ethanethiol promoter (1.2 equiv), followed by in situ reduction with Et_3SiH (1.2 equiv). Under these optimized conditions, diarylmethane **52** was isolated in 80% yield (Scheme 4, eq 1).

The attachment of secondary alkyl substituents to aromatic compounds is also facilitated by using our simple strategy, as exemplified by the coupling of arene **1d** with isobutyraldehyde (**2d**) followed by in situ selective oxidation (H_2O_2 at 0 °C)[15] to furnish sulfoxide **53** in 55% yield (Scheme 4, eq 2). The latter sulfoxide is a good leaving group under our reaction conditions, and nucleophilic substitution with allyltrimethylsilane afforded secondary alkyl substituted arene **54** in 78% yield. In a similar manner, selective oxidation of sulfide **3** followed by reaction with **1d** or a $TMSN_3$ (eq 3) provided a direct entry to triarylmethane **55** (89% yield) and benzylazide **56** (87%).[16] These examples further highlight the applicability of this novel chemistry to produce complex structures in a direct metal-free fashion.

In conclusion, a simple means to introduce primary alkyl groups onto aromatic compounds was developed. The multicomponent reaction is based on aromatic electrophilic substitution of aldehydes in the presence of thiol promoter, followed by either reduction or functionalization of the obtained benzylsulfide intermediates. This reductive alkylation reaction is general, extremely simple, highly chemo- and regioselective, and

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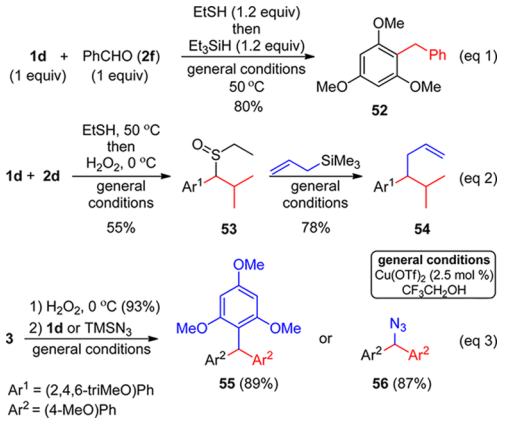
Scheme 4. Preparation of Diarylmethane 52 under Improved Atom Economy Conditions (eq 1) and Nucleophilic Substitution of Benzylsulfoxides under Our General Reaction Conditions (eq 2 and 3)



does not produce toxic waste. It can be carried out in air and in the presence of water and functional groups that are reactive toward the classic Friedel–Crafts conditions. We are certain that this method will find many uses in academic research and industrial applications, as it offers a practical solution that meets the challenge facing modern chemistry to solve one of the oldest synthetic problems in organic chemistry, the introduction of primary alkyl groups into aromatic compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01142.

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Notes

The authors declare no competing financial interest.

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