Photo-induced Formation of Cubyl Arylthioethers, Synthesis of mono Cubyl Analogue of Dapsone

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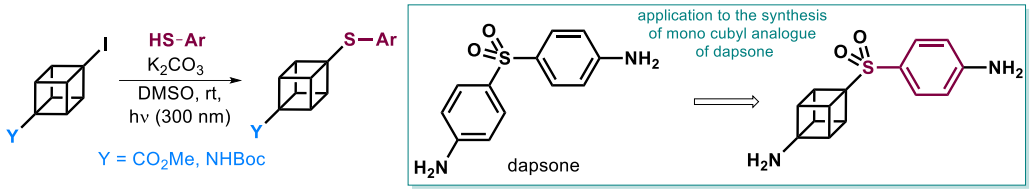
Supporting Information Placeholder



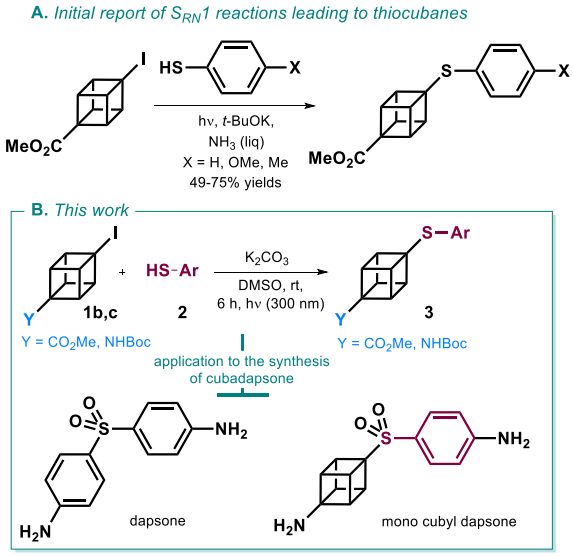
ABSTRACT: 1,4-Disubstituted cubyl arylthioethers were generated from the corresponding iodocubanes and aryl thiolates upon UV-irradiation in dimethylsulfoxide at room temperature. This simple procedure was found compatible with a variety of substituted aryl thiolates substituted. This finding paved the way to a synthesis of the mono cubyl analogue of dapsone, a key molecule in the treatment of leprosy, also known as Hansen's disease, and of acne.

Since Eaton's pioneering work,[1] the unique structure of cubane, as a 3D-bioisostere of benzene, has attracted considerable attention in the recent years.[2] Ingenious methods were devised for innovative functionalization[3] or for rearrangements[4] of the ring structure, thereby opening new chemical space. From the commercially available 1,4-dimethylcarboxylate cubane,[5] recent efforts were directed to the grafting of heteroatoms to the motif in order to reach a wide structural diversity.[6] The installation of sulfur to molecular scaffold is particularly important, as attested by the large number of molecules containing this element and with biological activities.[7] Furthermore, thioethers are precursors for sulfoxides, sulfoximines and sulfone after oxidation.

Access to cubanethiols has been complicated by the lability of the compound, and the focus shifted toward the preparation of dicubyl disulfide and cubyl thioethers.[8] To that end, the strategies encompass either the formation of lithiocubane that react with electrophilic sulfur[9] or the substitution with a nucleophilic sulfur reagent. While the first requires the structure of both reagents to be compatible with strong bases, the second strategy is not trivial as the structure of cubanes forbids an S_N2 reaction. Even though substitution reactions remain possible by solvolysis (S_N1) of either cubyl triflate or iodide in methanol or acetonitrile,[10,11] it is unknown and unpractical with thiol nucleophile. On the other hand, $S_{RN}1$ reaction (radical nucleophile unimolecular) involving a radical chain mechanism holds promise for assembling thiol nucleophile to the cubyl motif. Hence, focusing on the mechanism, Jimenez reported the coupling of methyl-4-iodocubane-1-carboxylate **1** under UV-activation with thiophenol, 4-methoxythiophenol and 4-methylthiophenol as nucleophiles (Scheme 1A).[12] The limited number of nucleophiles and the restricting conditions (NH_3 liquid) however impeded access to broader molecular diversity.

This aspect is of paramount importance for enabling the cubane motif to fully reach agrochemical and pharmaceutical studies as a bioisostere of benzene.[13]

Scheme 1.



Our interest in the cubane motif led us to develop the preparation of cubyl arylthioethers through a strategy involving $S_{RN}1$ of 4-iodoocubyl either substituted by 1-methoxycarbonyl or 1-aminocarbamate (NHBoc) groups.

Upon UV-exposure, variously functionalized thioaryl nucleophiles were simply assembled to the cubane motif at room temperature in DMSO. To illustrate the potential of the method, the synthesis of 1,4-disubstituted cubanes was extended to the mono cubyl analogue of dapsone, a molecule with known antiobiotic properties.

Simply prepared by a reaction of Hunsdiecker-Borodin (I_2, $PhI(OAc)_2$) of the commercially available carboxylic acid **1a** (Scheme 2), iodocubane **1b** was obtained in high yield (87%). To understand the reactivity of **1b**, we assessed the stability of the reagent under UV-irradiation at 300 nm (17 h) in anhydrous DMSO, a polar solvent (Table 1, Entry 1). This resulted in the formation of the reduced cubane **4** in 10% yield. A similar experiment in cyclohexane, a non-polar solvent, left the starting materials mostly unaffected, which is indicative that polar solvents increase the rate of the reductive process (Entry 2). The visible-light induced reduction of aryl halides without metals has been reported[14] and the formation of **4** attested that iodocubanes are sensitive to these conditions in polar solvent. In the context of our study, however, this experiment underlined the competition ahead of us between the substitution reaction and the reductive process.

Scheme 2.

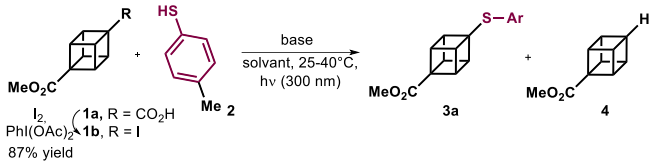


Table 1

Entry	Solvent	Base	1b/3a/4[a]	3a[b]
1[c]	DMSO	n/a	90/-/10	n/a
2[c]	cyclohexane	n/a	100/-/traces	n/a
3[d]	DMSO	*t*-BuOK	0/66/33	48%
4[e]	DMSO	*t*-BuOK	100/0/0	-
5[d,f]	DMSO	*t*-BuOK	0/100/traces	68%
6[d,f]	Acetone	*t*-BuOK	0/68/32	-
7[d,f]	DMF	*t*-BuOK	0/73/23	-
8[d,f]	CH_3CN	*t*-BuOK	0/65/35	-
9[f,g]	DMSO	K_2CO_3	0/100/traces	81%
10[f,g,h]	DMSO	K_2CO_3	87/0/13	-
11[f,i]	DMSO	K_2CO_3	0/77/23	-
12[f,i]	DMSO-d_6	K_2CO_3	0/82/18	-

[a] measured by ^{1}H NMR (300 MHz) of the crude reaction; [b] isolated yield; [c] without **2** and base (17 h); [d] 22 h of reaction; [e] without UV-exposure, at 50°C for 3 h; [f] in situ deprotonation; [g] 6 h of reaction; [h] in the presence of *m*-dinitrobenzene (2 equiv); [i] 365 nm instead of 300 nm, 4 h of reaction

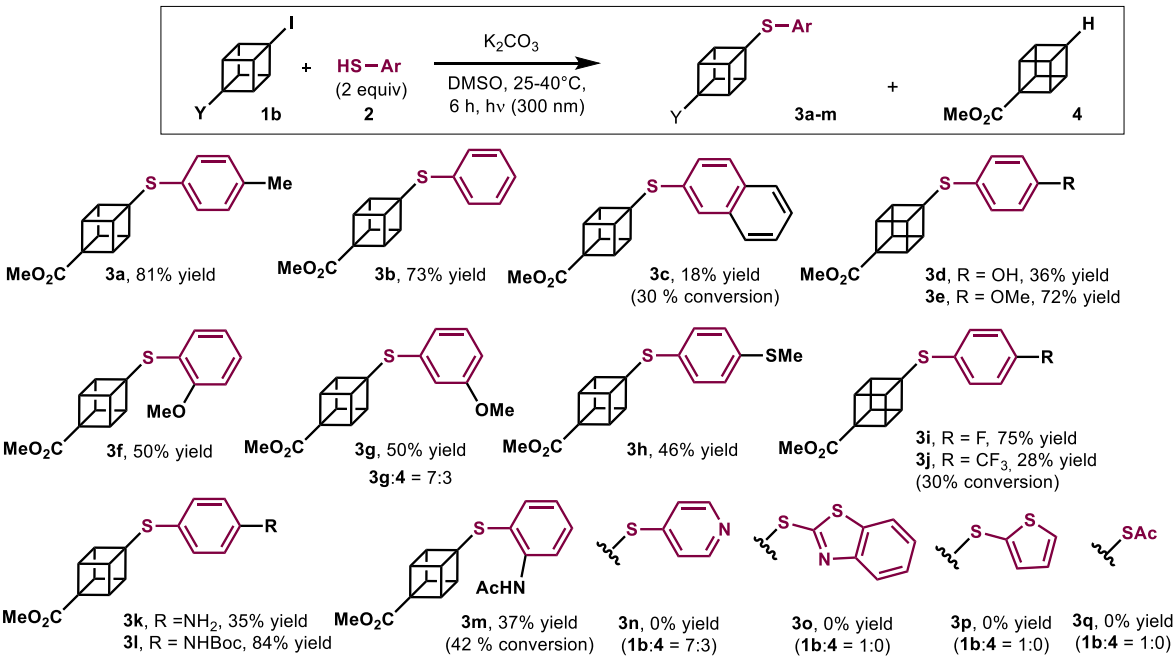
Pleasingly, the coupling reaction of 4-methylphenylthiolate **2** (4 equiv) with **1b** was faster than the reductive process which remained nevertheless a competitive pathway (Entry 3). After deprotonation of the thiol with *t*-BuOK, the reaction was left at rt under irradiation for 22 h and **3a** was isolated in 48% yield, whereas the ratio **3a**/**4** reached 66:33 in the crude reaction mixture. Note that performing the experiment at 50°C without UV-irradiation left the starting material unchanged (Entry 4). A protocol, in which the nucleophile (2 equiv) is in situ deprotonated, allowed the production of **3a** in higher yield (68 %) while suppressing the formation of **4** (Entry 5). Using this procedure, we then examined different polar solvents such as acetone, DMF and acetonitrile (Entries 6-8). In all cases, the amount of reduced cubane **4** was increased. While only traces of **4** were formed in DMSO, ^{1}H NMR of the crude reaction showed a ratio of 68:32 (**3a**:**4**) in acetone, of 73:23 (**3a**:**4**) in DMF and of 65:35 (**3a**:**4**) in acetonitrile. Switching to K_2CO_3 as the base in DMSO led to a complete conversion of **1b** in 6 h and an isolated yield of 81%, with only traces of **4** in the crude reaction mixture (Entry 9). On a larger scale (1 mmol) and without optimization, **3a** was isolated in 62% yield, as the amount of **4** was increased (**3a**:**4** =71:29). Performing the reaction in the presence of the electron acceptor *m*-dinitrobenzene (2 equiv, Entry 10) suppressed the formation of **3a** while the reductive process persisted, as attested by the production of **4** (**1b**:**4** = 87:13). The applied wavelength of the light source also influenced the selectivity, as operating at 365 nm led to a ratio **3a**:**4** of 77:23 (Entry 11). For the first time, the competitive reduction of **1b** was significant in DMSO and we were curious of the outcome when performing the reaction in deuterated solvent (DMSO-d_6). While the ratio **3a**:**4** was enhanced up to 82:18, the amount of **4** remained significant (Entry 12) without the noticeable formation of deuterated cubane **4**-*d*, which suggests that H-abstraction from the reagents is effective.

With a protocol in hand, we examined the scope of the chemistry beginning with the coupling of thiophenol which afforded thioether **3b** in 73% yield (Scheme 3). 2-Napthalenethiol was coupled to **1b** giving **3c** in 18% yield, a value to put in perspective with the non-optimized conversion of 30%.

Heterosubstituted thiophenols were next investigated as the nucleophilic character, enhanced by the heteroelement, was probably favorable for the substitution process. Without protection, 4-hydroxythiophenol was reacted with **1b** to yield **3d** (36%) and an equal amount of **4** but without indication that the corresponding *O*-ether was formed alongside the thioether. Protection of the phenol as methoxyether increased the yield to 72% in compound **3e**. The position of the substituent has an impact on the efficiency of the coupling, as attested by the coupling of 2-methoxythiophenol to **1b** in 50% yield alongside **4** in 25% yield. The fair yield in **3f** could be attributed to the steric hindrance of the *ortho*-substituent of the nucleophile. Interestingly, the substitution reaction was similarly effective with 3-methoxythiophenol as the thioether **3g** was isolated in 50% yield, noting also the production of **4** (**3g**:**4** = 7:3, determined by ^{1}H NMR spectroscopy). 4-Thiomethylthiophenol was coupled to the cubyl scaffold in 46% yield, the efficiency of the coupling being impeded by a difficult purification of **3h**.

As for halosubstituted thiophenol, 4-bromo and 4-chloro substituted nucleophiles were poorly compatible, whereas 4-fluorothiophenol was very efficiently coupled to the scaffold since compound **3i** was isolated in 75% yield. This indicates that the C-F bond is fully compatible with the $S_{RN}1$ strategy and that the fluorine mesomer effect induced a good reactivity of the nucleophile. Furthermore, 4-(trifluoromethyl)thiophenol was assembled to cubane in 28% yield (**3j**), the non-optimized conversion (30%) being impacted by the low nucleophilic character of the reagent due to the inductive effect of the CF_3 group. Nonetheless, these values attest of a very clean coupling reaction.

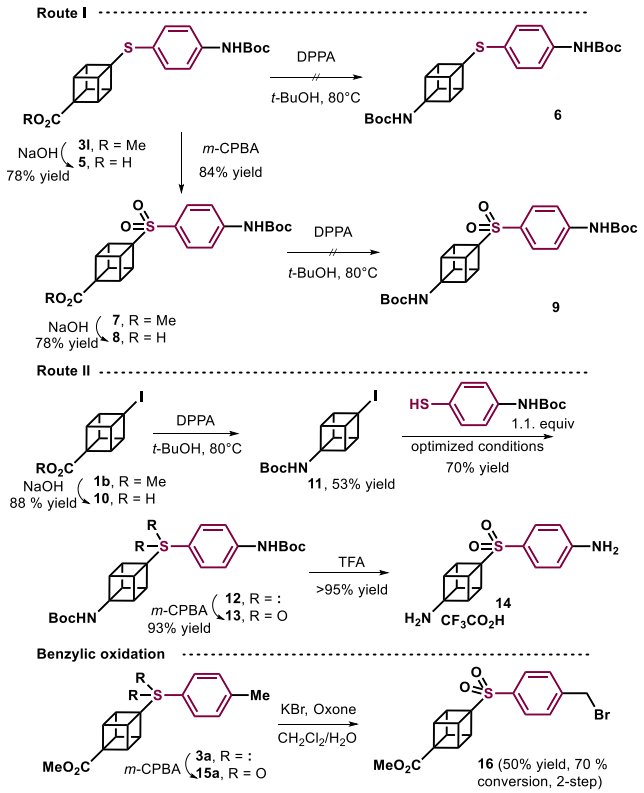
Scheme 3. Scope of the method



Aminothiophenols were next screened as the versatility of the amino group allows for facile functionalization. The unprotected 4-aminothiophenol was coupled to **1b** in 35% yield of **3k** alongside 20% of **4**, after a conversion of 74%. On the other hand, the *N*-Boc analogue was smoothly converted into the cubyl thioaniline **3l** in 84% yield, the highest value of the study. 2-(*N*-acetylamino)thiophenol was coupled to **1b** to give **3m** in 37 % yield in a conversion of 42% (2 runs). As previously noted with 2-methoxythiophenol, the steric hindrance of the nucleophile slows the conversion but the coupling of 2-(*N*-acetylamino)thiophenol remains synthetically useful. When 4-thiopyridine was employed as a nucleophile, the procedure led to **4** instead of thioether **3n**, with a ratio **1b**:**4** of 7:3 (determined by ^{1}H NMR spectroscopy). 2-Mercaptobenzothiazole was also tested in these conditions but no conversion was noted and the starting material was recovered, a similar result being observed with 2-thiophenethiol. The salt of thioacetic acid was also unreactive toward **1b** and the starting material was mostly unaffected.

To illustrate the versatility of the chemistry, we undertook the synthesis of the mono cubyl derivative of dapsone, a molecule employed in the treatment of leprosy and acne (Scheme 4). We initially set out a plan that would take advantage of thioether **3l**. Saponification (NaOH) led to **5** in 78% yield, setting the stage for performing the Curtius rearrangement (diphenylphosphoryl azide (DPPA), *t*-BuOH). However, all efforts to reach amine **6** were unsuccessful and led instead to a loss of material. In an attempt to facilitate the rearrangement, the thioether **3l** was oxidized into sulfone **7** with *m*-CPBA (84% yield). After saponification (78% yield), conditions were applied to trigger the desired Curtius rearrangement of **8**. Unfortunately, the same outcome was noted, a clean access to the amino cubane **9** remaining to be developed. To that end, a second route was devised from 4-(*N*-Boc-amino)-1-iodocubane **11** that would be exposed to 4-(*N*-Boc-amino)thiophenol (1.1 equiv) in the conditions of the coupling. Noting that **11** was prepared uneventfully (53% yield) by a Curtius rearrangement of **10**, we were even more delighted to observe a very clean conversion of **11** into the thioether **12** (70% yield). This is noteworthy since reactions following an $S_{RN}1$ mechanism usually perform better with electron-withdrawing groups on the carbon, or the aromatic ring, bearing the leaving group.

Scheme 4.



Subsequent oxidation of the thioether led to sulfone **13** in 65% yield (2-step). Deprotection of the Boc groups (TFA) concluded the synthesis with **14** obtained in quantitative yield.

In addition, the selective benzylic oxidation of **15a** was demonstrated in the mild conditions developed by Moriyama and Togo.[15] Prior conversion of the sulfide **3a** into sulfone **15a** was followed by the oxidation of the benzylic position giving **16** in 50 % yield (2-step) after a conversion of 70%.

From a mechanistic perspective, we were curious to determine whether aryldisulfides or alkylthiols could react with **1b**. To that end, $(PhS)_2$, ethyl thioglycolate or *i*-propanethiol were tested but no thioether was formed in all cases.[16] Instead, the reduced cubane **4** was noted in significant amount. Subsequent to this observation, a second run was conducted to obtain a complete conversion of **1b** into **4**, thereby providing a practical and alternative route to reduced cubanes.

A simple and convergent approach to cubyl arylthioethers was developed under UV-irradiation (300 nm) in a 2-step sequence from commercially available cubyl material. Despite the competitive reductive process, the method was demonstrated with an array of substituted arylthiols paving the way to unprecedented molecular spaces. The method tolerates a good variety of aryl substituents, acylated amino being the most salient. Although electron-poor arylthiols are not efficient in the coupling reaction, we demonstrated that oxidation of the benzylic position of **15a** is effective, overcoming somehow this limitation. Eventually, we have demonstrated that **11** is a very good partner for the coupling reaction, which further extends the scope of the method and enables additional functionalization. This feature was crucial to develop a route to a medicinally pertinent mono cubyl derivative of dapsone,

ASSOCIATED CONTENT

• Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

• Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.
General procedure and characterizations of each compounds, as well as optimization of the procedure and copies of ^{1}H, ^{13}C NMR spectra. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: **3a**-**3m**, tert-butyl (4-((4-((tert-butoxycarbonyl)amino) phenyl)thio)cuban-1-yl)carbamate, **5**, **7**, **8**, 4-iodocubane-1-carboxylic acid, tert-butyl (4-iodocuban-1-yl)carbamate, tert-butyl 4-((4-((tert-butoxycarbonyl)amino)phenyl)sulfonyl)cuban-1-yl)carbamate, **14** and **16**.

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