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Study Toward the Undirected Fluorination and Chlorination of Cubane 1,4-Diester

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Abstract

Study toward the undirected fluorination and chlorination of cubane 1,4-diester is described by C-H activation using friendly-user reagent such as Selectfluor and dichlorodimethyl hydantoin under photoinduction. While the fluorocubane 1,4-diester is formed in low yield (8% yield) due to loss of material, the chlorocubane 1,4-diester was on the other hand prepared in good yield (59%, 76% conversion) without the need of photocatalyst. Moreover, the chlorination of the strained scaffold was developed using flow technology.

Keywords

fluorination; chlorination; cubane 1,4-diester; C-H activation; photoactivation

Introduction

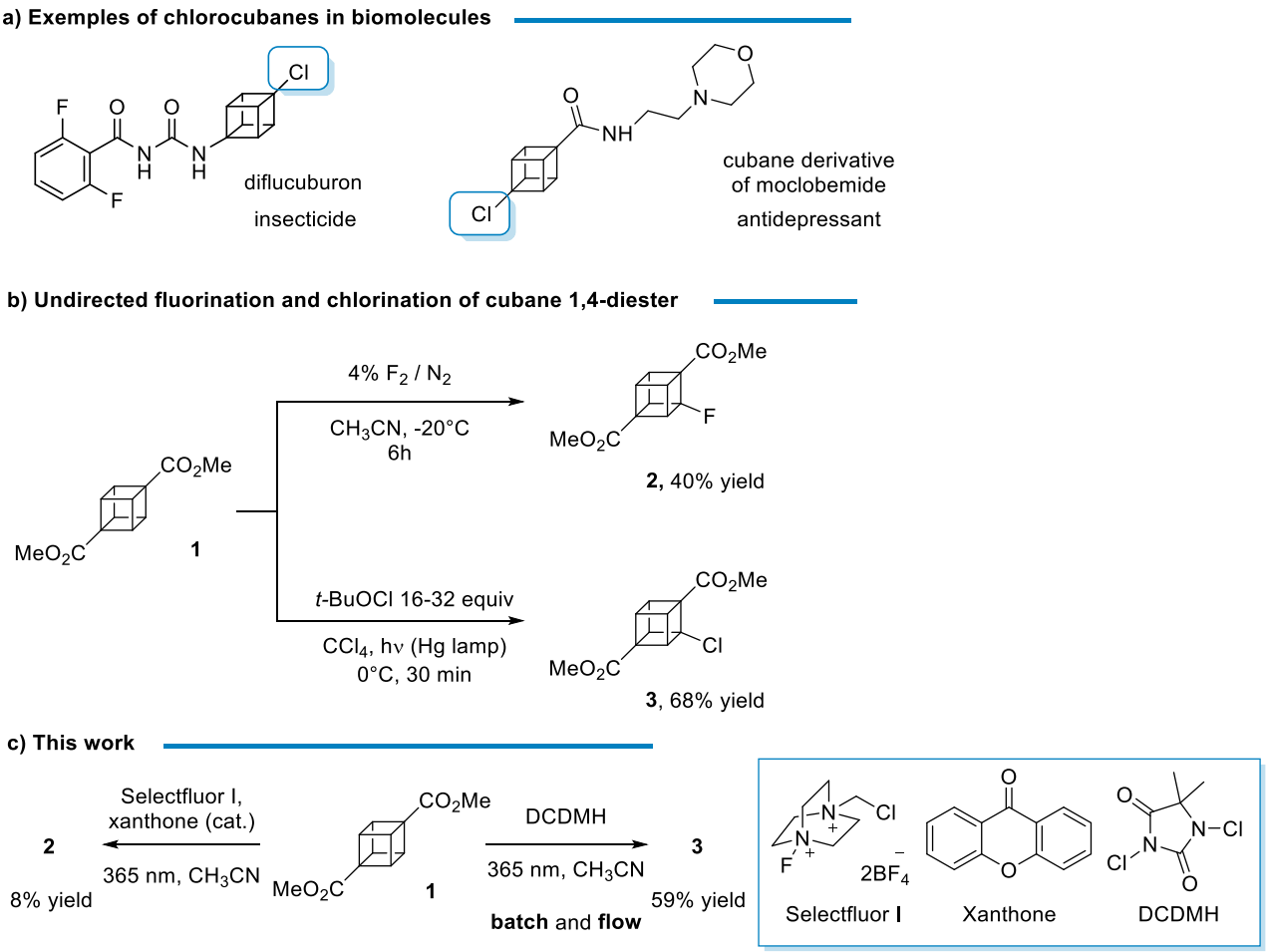
The strained cubane scaffold, originally synthesised by Eaton, serves as a three-dimensional bioisosteric alternative to benzene, sharing similar dimensions but lacking π-character [1]. Functionalization of the commercially available cubane 1,4-diester is a critical step to obtain isosteres of trisubstituted benzene rings in molecules of interest. Of note, molecules incorporating the cubane motif often exhibit enhanced solubility, metabolic stability, nonspecific binding and biological activity compared to their aromatic counterparts [2-5].

Among the functionalization strategies, halogenation — particularly fluorination and chlorination — represents a powerful tool for modulating physicochemical properties of aromatic rings, including acidity, halogen bonding, metabolic stability, and solubility [6-7]. The chlorocubane motif can be found in biomolecules with interesting biological properties like diflucuburon and the cubyl analogue of moclobemide (Scheme 1a) [8].

As 1,4-disubstituted halocubane derivatives are prepared by halodecarboxylation, the synthetic routes to 1,2,4-trisubstituted halocubanes is lengthier requiring prior carboxylation of cubane 1,4-diester.

As an alternative route, the halogenation by hydrogen abstraction of cubane 1,4-diester remains difficult given the presence of ester groups inducing strong C–H bonds (103 kcal.mol^{-1}) to the framework, as highlighted by Della and Walton [9].

Accordingly, the undirected fluorination or chlorination of cubane 1,4-diester **1** by C-H activation requires harsh conditions (Scheme 1b). The first one was reported in the presence of F_2 in 40% yield [10] while the photoinduced chlorination in 68% yield was recently documented by Kaleta under exposure to an excess of *t*-BuOCl in CCl_4 [11].



Scheme 1: Undirected fluorination and chlorination of cubane 1,4-diester **1**.

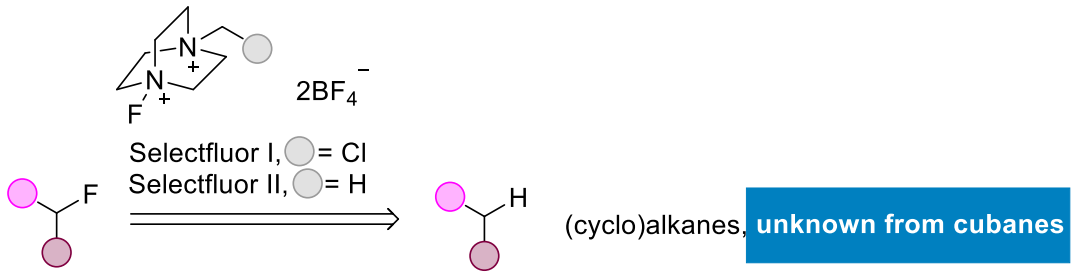
When one considers performing the monohalogenation of the cubane 1,4-diester, there is a threefold challenge entailing 1) incomplete conversion, leading to potentially co-eluting mixture of starting material and halocubane 1,4-diester, 2) polyhalogenation or 3) degradation of the strained carbon cage.

We wish to describe herein our efforts to perform the fluorination and chlorination of cubane 1,4-diester by C-H activation with user-friendly, readily available reagents and solvents (Scheme 1c).

Results and Discussion

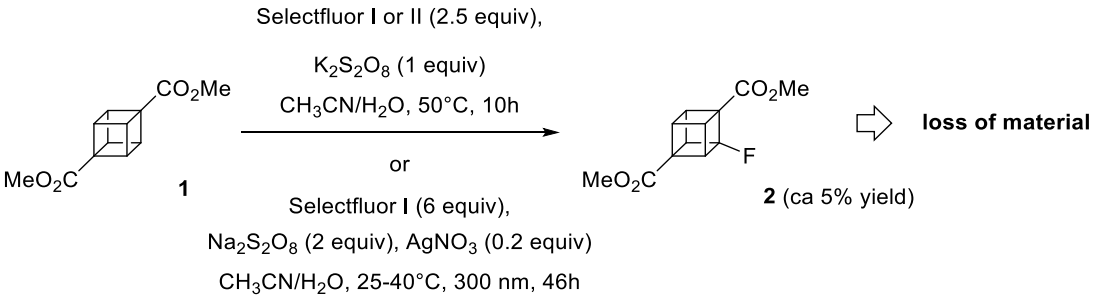
Fluorination of cubane 1,4-diester

The study began with the design of a new approach to the fluorocubane 1,4-diester **2** by the undirected fluorination of the commercially available cubane 1,4-diester with Selectfluor instead of fluorine gas. Selectfluor I and II, are practical sources of electrophilic fluorine, employed in undirected C-H fluorination of (cyclo)alkanes involving HAT mechanisms with [12-17] or without photocatalysts [18-19] (Scheme 2).



Scheme 2: Undirected fluorination of (cyclo)alkanes with Selectfluor reagents.

Exposing cubane 1,4-diester to Selectfluor I or II in the presence of peroxydisulfate salts upon heating or under photoactivation led to the production of a small amount of fluorocubane **2** alongside variable amount of remaining starting material, an important loss of material being noted (Scheme 3).

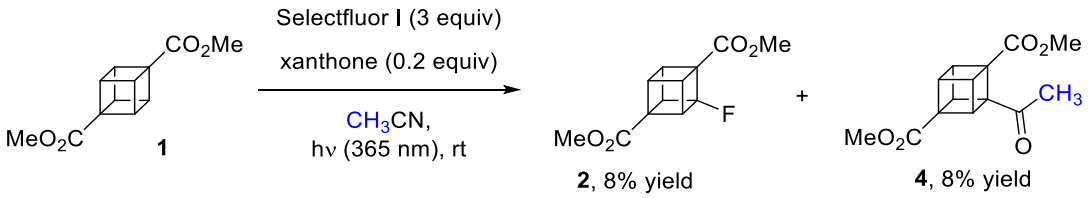


Scheme 3: Fluorination of **1** with Selectfluor I or II and peroxydisulfate.

Since slightly more side products were noted in the crude of the reaction with Selectfluor II, the first generation of reagent was preferred for the rest of the study. To

mitigate degradation, milder conditions were sought using photocatalysts. While attempts to perform the fluorination with tetracyanobenzene or TBADT were unsuccessful [21], the photocatalyst xanthone (20 mol%) at 300-350 nm gave slightly better results (Scheme 4) [20]. In the best scenario, however, the production of **2** reached 8% yield amid partial conversion. It must be underlined that the separation of **2** from the starting material is challenging and achieving higher conversion was detrimental to the mass balance.

As a possible explanation of the degradation, we isolated 2-acetylcubane 1,4-diester **4** in variable amounts (up to 8% yield). This product may come from the reaction of the cubyl radical with acetonitrile followed by hydrolysis of the resulting imine/enamine. Since acetyl, or the parent imine, can be fluorinated with Selectfluor I, it is possible that the fluorination of acetyl **4** or the imine precursor occurred, followed by degradation. The uncontrolled acetylation of fluorocubane **2** may take place as well. Note that no conversion was observed when operating in methanol instead of acetonitrile.

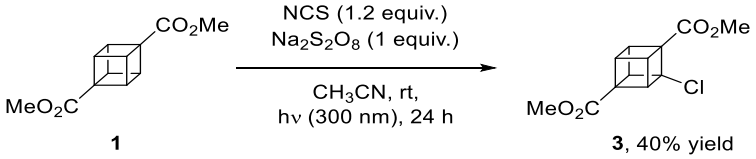


Scheme 4: Photoinduced fluorination of **1** with Selectfluor I and catalytic amount of xanthone.

In summary, the fluorination of cubane 1,4-diester was investigated with Selectfluor (I or II) and various photocatalysts, invariably leading to a small amount (8% yield) of fluorocubane 1,4-diester. As a possible explanation for the low mass balance, the formation of acetyl **4** hints to side reactions with the solvent. This observation moved us to develop a strategy of fluorodeiodination of iodocubanes with Selectfluor allowing a directed installation of the fluorine atom [22].

Chlorination of cubane 1,4-diester

Pursuing the halogenation of cubane 1,4-diester **1** with mild reagents, we sought to carry out the undirected chlorination of the material. After a screening of conditions, we identified reactions parameters inducing the smooth chlorination of **1**. As detailed in Scheme 5, N-chlorosuccinimide (NCS) was combined with photoexcited (300 nm) peroxydisulfate sodium salts to form chlorocubane **3** in 40% yield after 24h of reaction (70% conversion).



1 **3**, 40% yield

Scheme 5: Undirected photoinduced chlorination of **1**.

The contrast with the fluorination of **1** is noteworthy, there was no important loss of material and, probably related, the acetyl product **4** was not detected in the crude of the chlorination reaction.

From this initial result, we carried out an optimization of the reaction parameters (Table 2). Performing the experiment at 365 nm (Entry 2) was slightly better (44% yield) while increasing the concentration to C = 0.1 mol/L (Entry 3) enhanced conversion and yield (52%). On the other hand, higher concentration (Entry 4) was unfavorable. In a major shift, it was found that the use of sodium peroxydisulfate was slightly detrimental (Entry 5) and, unexpectedly, operating without the oxidant led to **3** in 57% yield (82 % conversion). A screening of solvent revealed that acetonitrile gave a better result compared to chlorinated solvents or acetone (Entry 6-9). Eventually, dichlorodimethylhydantoin (DCDMH) was more efficient than NCS (Entry 10), **3** being obtained in 59% yield and 76% conversion. Attempts to achieve higher conversion resulted in negative mass balance.

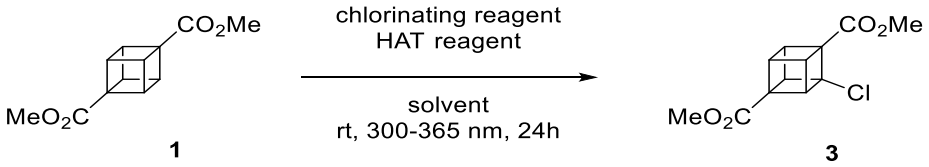


Table 2: Chlorination reaction of **1**.

Entry	Reagent	HAT reagent	Solvent	C (mol/L)	conversion	Yield
1 [a]	NCS [c]	$Na_2S_2O_8$	CH_3CN	0.05	70%	40%
2 [b]	NCS [c]	$Na_2S_2O_8$	CH_3CN	0.05	67%	44%
3 [b]	NCS [c]	$Na_2S_2O_8$	CH_3CN	0.1	72%	52%
4 [b]	NCS [c]	$Na_2S_2O_8$	CH_3CN	0.2	65%	48%
5 [b]	NCS [c]	-	CH_3CN	0.1	82%	57%
6 [b]	NCS [c]	-	CH_2Cl_2	0.1	55%	nd
7 [b]	NCS [c]	-	acetone	0.1	nr	
8 [b]	NCS [c]	-	DCE	0.1	nr	
9 [b]	NCS [c]	-	$CHCl_3$	0.1	nr	
10 [b]	DCDMH [d]	-	CH_3CN	0.1	76%	59%

[a] 300 nm; [b] 365 nm; [c] 1.2 equiv; [d] 0.7 equiv.

We next sought to develop the reaction of chlorination in flow conditions (in a Vapourtec® R-series) with both the aim to scale up and to evaluate the impact of the t^R (residence time) on the amount of polychlorocubane products (Table 3). In batch, small amount of polychlorocubanes was detected and we were curious to examine whether these products could be suppressed.

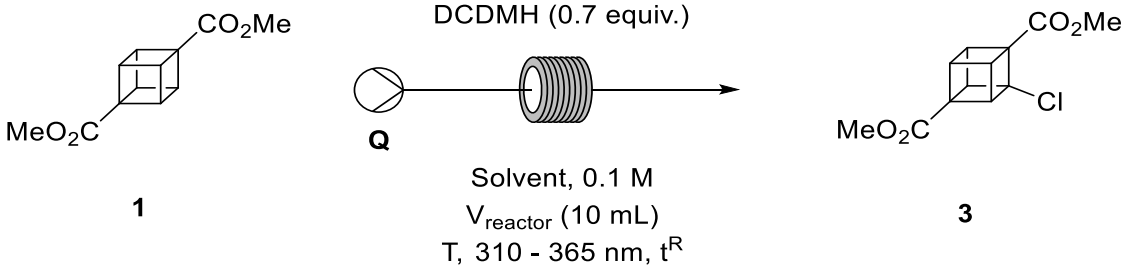


Table 3: Chlorination reaction of **1** in flow.

Entry	Flow rate Q (mL/min)	Solvent	T (°C)	t^R (min)	conversion
1 [a,b]	0.4	CH_3CN	28	25	-
2 [a,b]	0.4	CH_3CN/CH_2Cl_2 (10:1)	28	25	30%
3 [a,b]	0.4	CH_3CN/CH_2Cl_2 (4:1)	28	25	45%
4 [b,c]	0.22	CH_3CN	30	45	57%
5 [c,d]	0.22	CH_3CN	28	30	53%

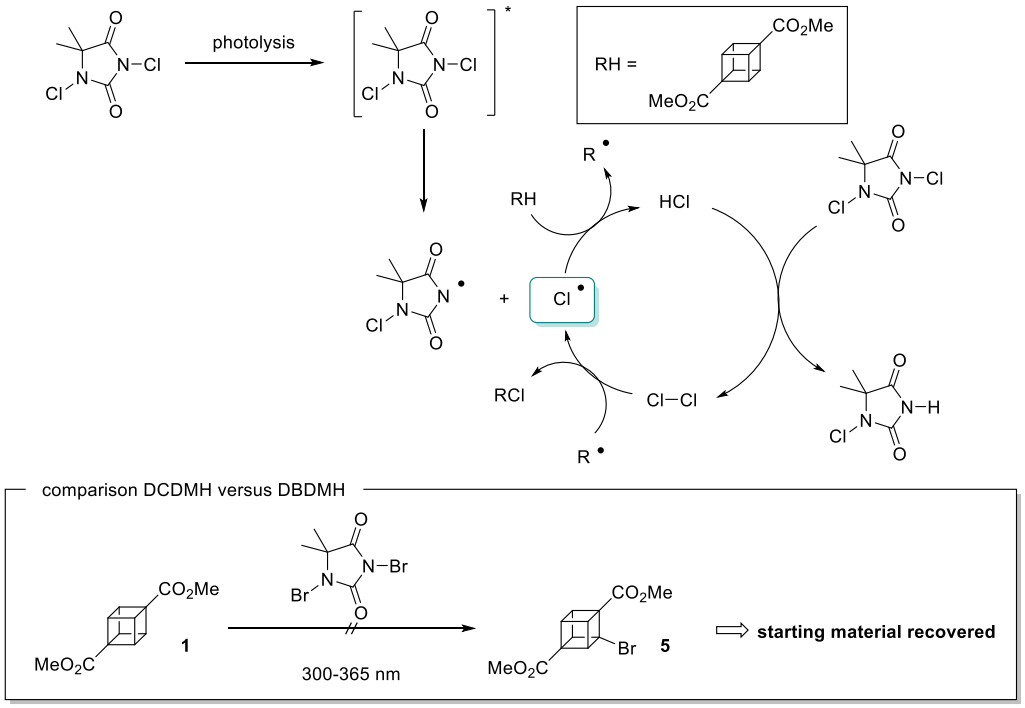
[a] partial precipitation; [b] 365 nm; [c] heating at 30°C and sonication of the solution of **1** (C = 0.1 M); [d] 310 nm

It was however noted that **1** partially precipitated in the tube, in solution of CH_3CN (flow of 0.4 mL/min, Entry 1), and a co-solvent CH_2Cl_2 was introduced (Entries 2,3). Even though partial solubilization of **1** was achieved, conversion of 30-45% (residence time of 25 min) was estimated, depending on the added amount of CH_2Cl_2. After 45 min of residence, higher conversion of 57% was obtained using a preheated and sonicated initial solution of **1** in CH_3CN. In these conditions, however, a small amount of polychlorinated cubanes was detected. A similar setting was tested at 310 nm (Entry 5) which led to a conversion of 53% and the isolation of **3** in a yield of 41% (61% BRSM).

While the chlorination of **1** was reported by Kaleta with a large excess of *t*-BuOCl (16-32 equiv) under photoactivation, the discrepancy with the current method involving DCDMH (0.7 equiv) is worth to be underlined. Given that DCDMH is the sole reagent required for chlorination and based on the ability of NCS to release chlorine radicals (•Cl) [23], it seems reasonable to postulate that cubane H-abstraction with the chlorine atoms resulted in HCl (BDE = 102 kcal.mol^{-1}) formation (Scheme 5) [24]. Note that cubane H-abstraction is a challenging transformation (BDE = 103 kcal.mol^{-1})

performed here with stable and available reagents DCDMH or NCS. The generation of cubyl radical from cubane 1,4-diester traditionally requires photoexcited strong and unstable oxidant, such as *t*-BuOX (X = Cl [11], I [25]), or tetra-*n*-butylammonium decatungstate (TBADT) [26-32]. When the experiment was conducted in the dark, the chlorination was quenched.

The reaction of HCl with DCDMH would generate chlorine allowing the formation of chlorocubane by reaction with cubyl radicals and subsequent generation of •Cl. In summary, the chlorination of cubane is enabled through the catalytic release of •Cl and Cl_2 from DCDMH.



Scheme 5: Proposed mechanism.

In contrast, exposure of **1** to dibromodimethylhydantoin (DBDMH) under photolysis (300-365 nm) left the starting material unchanged, which is in line with the strength of HBr bond (BDE = 87 kcal.mol^{-1}). As a matter of fact, the bromination of **1** requires a combination of DBMDH and photoexcited TBADT [32].

Conclusion

Mild conditions were developed to perform the undirected fluorination and chlorination of the commercially available cubane 1,4-diester, that will be of interest for the synthesis of substituted benzene isosteres. Whilst the fluorination route was limited in terms of efficiency compared to the fluorodeiodination strategy, user-friendly reagents and solvents were successfully employed for the chlorination reaction, showcasing the role of •Cl for cubane H-abstraction. The transformation was performed in batch and was extended to a flow setup. These advances should facilitate the incorporation of chlorocubyl materials into molecules in various fields of investigation spanning medicinal chemistry, material, and crop science.

Supporting Information

Supporting Information File: Synthesis description, characterization data and spectra

Acknowledgements

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