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Cyanuric chloride–dimethylformamide mediated cleavage of cyclopropylcarbinols-synthesis of phenolic antioxidant and construction of a new vinylcyclopropane skeleton

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ABSTRACT

Differently substituted cyclopropylcarbinols underwent ring cleavage with easily accessible cyanuric chloride–*N*,*N*-dimethylformamide adduct to produce homoallylic chlorides or dienes depending on the nature and location of the substituents. A mechanistic explanation of the aforesaid observations has been provided. A promising antioxidant compound was prepared following this protocol and studied against Fenton's reagent. This methodology was utilized to construct hitherto unreported vinylcyclopropane frameworks bearing homoallylic chloride and diene moieties.

Cyclopropane framework has drawn considerable interest in recent times among the synthetic organic chemists not only due to its occurrence as a subunit of numerous natural products[1] but also for its unique reactivity[2] associated with ring strain. Several important molecular skeletons have been efficiently constructed utilizing the cleavage of appropriately constituted cyclopropane motifs in well-defined fashions using a plethora of classical and upcoming reagents.[3] Various electrophilic reagents promote the so-called 'edge opening' of cyclopropane where an electron deficient centre is initially developed on the cyclopropylcarbinyl carbon followed by a ring scission.[4] As a result, a homoallylic moiety is generated which undergoes subsequent reactions (either attack by the nucleophiles[4a–c] or reductive transformations[4d]) depending on the composition of reagents. Dehydrative ring opening of cyclopropylcarbinols under thermal,[5a] ionic liquid-catalysed sonochemical condition[5b] and indium triflate catalysed reaction[5c] produce 1,3-dienes.

Recently, cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, to be called TCT hereafter) has come out as an efficient solid reagent for important organic transformations. It can be conveniently handled and it is relatively less toxic compared to many other reagents of similar kind. This reagent was used over the last few years as an activator[6a] during the reduction of carboxylic acid to primary alcohol, as a chlorinating agent[6b] in the preparation of sulfonyl chlorides from sulfonic acids, as a coupling agent[6c] during the synthesis of hydroxamic acids from carboxylic acids, as a catalyst for ammonium thiocyanate-mediated solvent-free conversion of thiiranes[6d] from oxiranes, as π-spacer[6e] during the synthesis and photovoltaic studies of donor-π-acceptor dyes, as a promoter[6f] for the labelling of mouse anti-quail IgY with horseradish peroxidase, as a catalyst[6g] for the Pictet–Spengler reaction with electron-donating aldehydes and as a reagent[6h] for activating DMSO during the structure-dependent conversion of various alcohols to methylene acetal, thioether, and ene-thioether. TCT in combination with DMF was utilized as a mild chlorinating agent for the conversion of alcohols and β-aminoalcohols to the corresponding alkyl chlorides,[7a] regioselective synthesis of unsymmetrical allyl chlorides through *ipso*- and *tele*-substitution[7b] and construction of 2-azetidinone[7c] moieties. Inspired by the aforesaid literature precedence we initiated a detailed investigation on the cleavage of differently substituted cyclopropylcarbinols with TCT–DMF adduct[7a] at room temperature.

Different chalcones were prepared through the base-promoted condensation of substituted aryl methyl ketones with various aryl aldehydes in the presence of alcoholic NaOH[8a] and subsequently cyclopropanated using dimethylsulfoxonium methylide which

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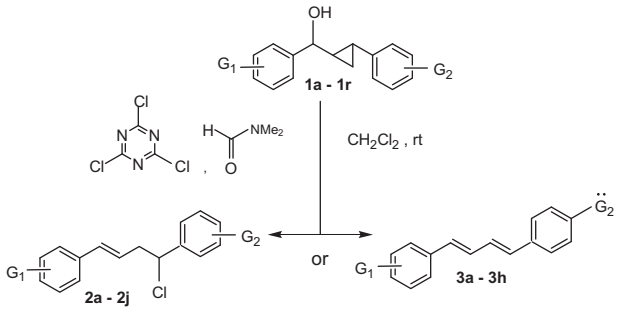


Scheme 1. Reaction of **1** with TCT–DMF.

was generated by the deprotonation of trimethylsulfoxonium iodide with alkali under phase transfer condition using a phase transfer catalyst.[8b] Further reduction of the cyclopropyl ketones with methanolic sodium borohydride at room temperature produced the cyclopropylcarbinols **1** with appropriately substituted aryl rings at the carbinol carbon as well as one of the cyclopropyl carbons. Differently substituted cyclopropylcarbinols **1** reacted with easily accessible TCT–DMF adduct[7a] in anhydrous dichloromethane to produce the homoallylic chlorides or dienes depending on the electronic nature and location of the substituents (Scheme 1). Results are presented in Table 1.

As with **1a** having no substituent at the aromatic ring (entry 1), cyclopropylcarbinols (**1b**, **1c**, **1g** and **1h**) bearing electron-donating groups at the aromatic ring of the carbinol centre produced the corresponding homoallylic chlorides **2b**, **2c**, **2g** and **2h** in good yields (entries 2, 3, 7 and 8). It is important to note that **1d** (with electron-withdrawing substituent at the aromatic ring connected to the carbinyl carbon) underwent the cleavage of cyclopropane ring to produce **2d**. Compounds **1e**–**1h** bearing electron-withdrawing groups at the aromatic ring attached to the cyclopropane ring also produced the corresponding homoallylic chlorides **2e**–**2h** in good yields. Homoallylic chlorides **2i** and **2j** were also obtained from the compounds **1i** and **1j**, carrying an electron donating group (OMe) at the *m*- and *o*-positions respectively of the aromatic substituent of the cyclopropane motif. Notable advantages of the present method seem to be an exclusive formation of ring-cleaved products without detectable (by ^{1}H NMR) formation of the cyclopropyl products arising out of normal substitution and cyclobutyl derivatives by the Demjanov rearrangement through the intermediacy of non-classical carbonium ions.[11]

Homoallylic chlorides have attracted the attention of synthetic organic chemists due to their versatility as substrates in organic synthesis,[12a] occurrence as sub-units of many natural and unnatural products[12b–e] and important applications in pharmaceutical and agrochemical industries.[12f] But there are only a few reports[13] for the synthesis of homoallylic chlorides which have limited applicability due to the tedious experimental set-up and vulnerability of the products to further side reactions. Preparation of homoallylic chlorides from appropriate homoallylic alcohols often leads to the formation of complex mixture of products due to allylic rearrangement and polymeric decomposition. The present method provides an easy access to unsymmetrical homoallylic chlorides from easily accessible precursors using commercially viable reagents.

Interestingly, in the substrates where the cyclopropyl moiety carried an aromatic ring with the electron-donating group at *p*-position (**1k**–**1r**), conjugated dienes (**3a**–**3h**) were obtained exclusively instead of the homoallylic chlorides (entries 11–18 in Table 1). Conjugated dienes and polyenes are not only present as a structural sub-unit in many bio-active natural products[14a] but also have immense potential for the design of optical power limiting organic materials used to manufacture various laser safety devices.[14b,c] 1,3-Butadiene moiety serves as a versatile building block for the construction of complicated molecular skeletons through the Diels–Alder reaction.[14d] Although there are literature reports[5,10,15] for the synthesis of 1,3-dienes, yet many of them involve exotic and toxic reagents. As shown in Table 1, the present protocol provides a facile and cost-effective access to a number of structurally and functionally important[10a–e] dienes [entries 11, 12, 14–16] without using exotic reagents[5] and complicated experimental procedure. The acid-labile moieties like benzyl (entry 13) and methylenedioxy (entries 16–18) survived during the said transformation. In every occasion, the diene **3** was obtained from the cyclopropylcarbinol with the aromatic ring carrying an O-alkyl substituent at *p*-position irrespective of whether the carbinyl carbon carries an aromatic ring with electron-donating (entries 12, 13, 17) or electron withdrawing (entries 14, 15, 18) substituents at *p*-position. The cyclopropylcarbinol **1g** produced the homoallylic chloride **2g** on treatment with TCT–DMF (entry 7). In contrast to the aforesaid observation, the isomeric cyclopropylcarbinol **1o** (with the positions of electron-donating and electron-withdrawing groups interchanged) produced the diene **3e** (entry 15) instead of the corresponding homoallylic chloride. Apart from the distinction by ^{1}H NMR signals, the formation of diene **3e** was further

Table 1
Reaction of cyclopropylcarbinol **1** with TCT–DMF

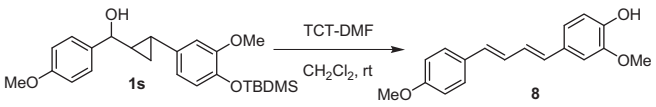
Entry	G_1, G_2	Substrate (**1**)	Product (**2**/**3**)	Time (h)/yield[a] (%)
1	H, H	**1a**	**2a**	4/88[9]
2	4-OMe, H	**1b**	**2b**	5/82
3	4-Me, H	**1c**	**2c**	5/84
4	4-NO_2, H	**1d**	**2d**	4/80
5	H, 4-Cl	**1e**	**2e**	7/79
6	H, 4-NO_2	**1f**	**2f**	4/81
7	4-OMe, 4-NO_2	**1g**	**2g**	4/87
8	4-OMe, 4-Cl	**1h**	**2h**	5/86
9	H, 3-OMe	**1i**	**2i**	6/80
10	H, 2-OMe	**1j**	**2j**	6/79
11	H, 4-OMe	**1k**	**3a**	12/83[10a]
12	4-OMe, 4-OMe	**1l**	**3b**	12/81[10b]
13	4-OMe; 3-OMe, 4-OCH_2Ph	**1m**	**3c**	15/76
14	4-Cl, 4-OMe	**1n**	**3d**	14/80[10c]
15	4-NO_2, 4-OMe	**1o**	**3e**	14/82[10d]
16	H, 3,4-OCH_2O–	**1p**	**3f**	12/75[10e]
17	4-OMe, 3,4-OCH_2O–	**1q**	**3g**	12/78
18	4-NO_2, 3,4-OCH_2O–	**1r**	**3h**	11/81

[a] Yield refers to isolated pure products fully characterized spectroscopically.

established from the UV analysis, which showed a strong band with λ_{max} at 401.83 nm (ε 15,210) for π–π^* transition due to the development of extended conjugation. So, it is evident that although the initial cleavage pattern of the cyclopropane ring remains uniform irrespective of the nature and location of the substituents in the aryl rings yet the final outcome of the reaction is critically dictated by the two aforesaid factors.

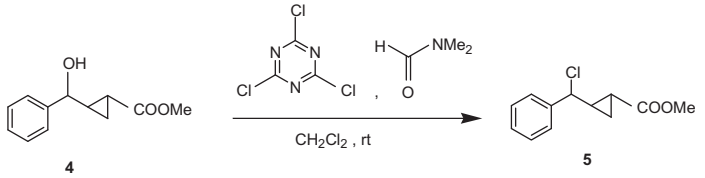
Cyclopropylcarbinol **4**[16] carrying the $COOCH_3$ group (an electron-withdrawing substituent) at the ring carbon under similar treatment neither produce any homoallylic chloride nor the diene (as evident from its ^{1}H NMR spectrum); rather, cyclopropane ring remained intact with the formation of chloro substituted product **5** (Scheme 2).

A plausible mechanism is presented in Figure 1 to account for the effect of the substituents towards the reaction outcome. The relief of strain in the cyclopropane ring due to its opening to the acyclic system along with the attainment of the extended conjugation of the newly developed double bond with the aromatic moiety seems to be the driving force for this transformation. According to Figure 1, cyclopropylcarbinol **1** reacts with TCT–DMF adduct[7a] to produce **6** where a partial electron deficiency at the carbinol centre is developed. Concomitant cleavage of the cyclopropane ring in **6** with departure of DMF as a leaving group forms carbocation **7** as an intimate ion pair. Compound **2** is obtained from **7** through the capture of Cl^-. When the carbocation **7** is mesomerically stabilized by the electron-donating substituent G_2 located at the *p*-position (canonical **7′**), development of more positive charge on a carbon makes the adjacent C–H bonds of the $-CH_2-$ moiety in **7** more acidic. Therefore, subsequent deprotonation even under weakly basic condition yields the diene **3**. As the cleavage of the cyclopropane ring is triggered by the supply of electron density to the initially developed electron-deficient centre from the cyclopropane ring in **6**, the electron-withdrawing group (like $-COOCH_3$) cannot assist in this way; rather it impedes this initial electron donation. So the cyclopropane ring in **4** survives in this reaction and it is converted to the corresponding chloride **5** (Scheme 2) through usual nucleophilic substitution.[7a]



Scheme 3. Synthesis of compound **8**.

Development of various cardiovascular and malignant diseases is often linked to the processes associated with damages of biological systems caused by reactive oxygenated species. Naturally occurring phenolic antioxidants such as vitamin E,[17a] curcumin[17b,c] and resveratrol[17d] as well as synthetic analogues such as BHT[17a] prevent radical reactions by terminating radical chain mechanisms which are responsible for cellular damage and oxidative spoilage both in vivo and in vitro. Radicals abstract a hydrogen atom from the phenolic OH group of the antioxidant and form a resonance-stabilized phenoxy radical which halts the oxidation process. The antioxidative[17e] and antiproliferative[17f] properties and inhibitory capacity of such compounds are critically dictated by the number and position of hydroxyl groups as well as the presence of certain chemical groups and double bond(s) at particular locations. A phenolic compound where the resultant phenoxy radical would be further stabilized due to extended conjugation through a diene moiety along with an aptly placed dative OMe group might be



Scheme 2. Survival of cyclopropane ring.

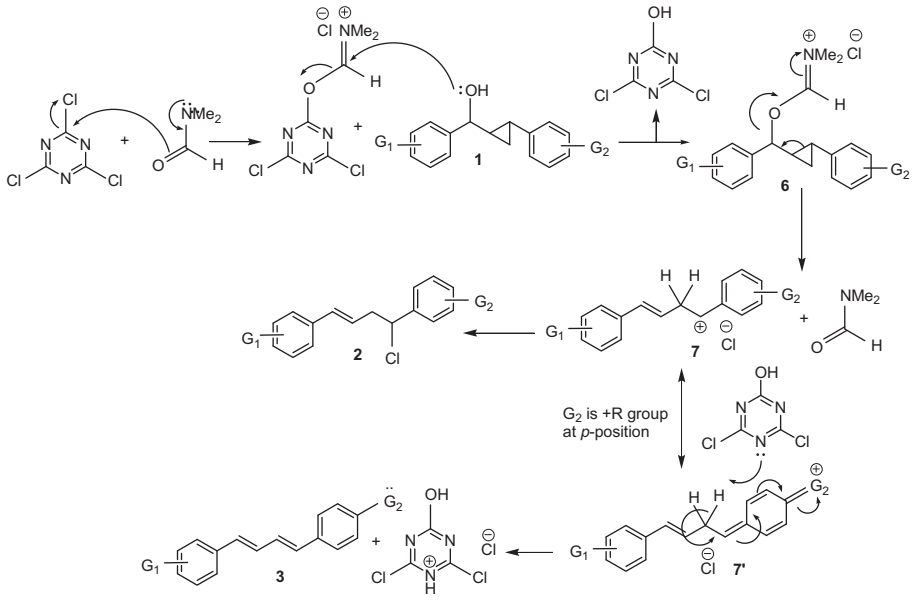


Figure 1. Mechanistic explanation for the substituent effect.

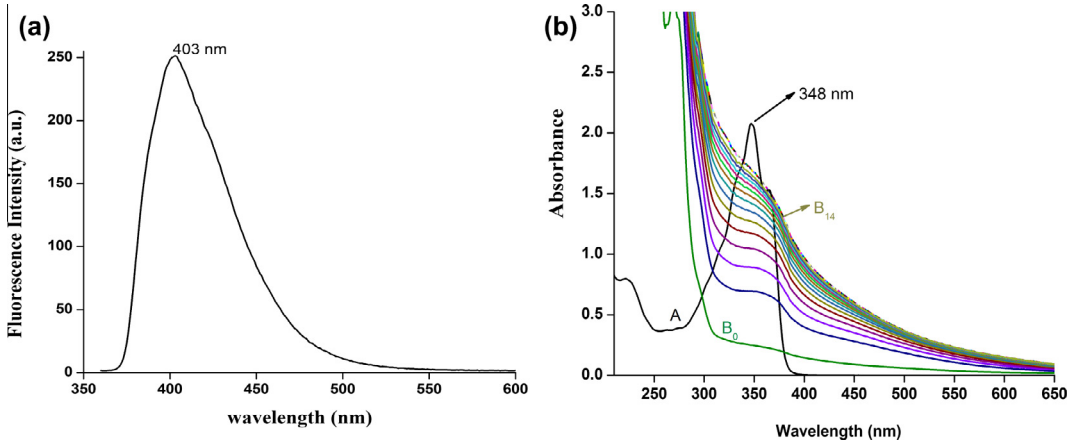
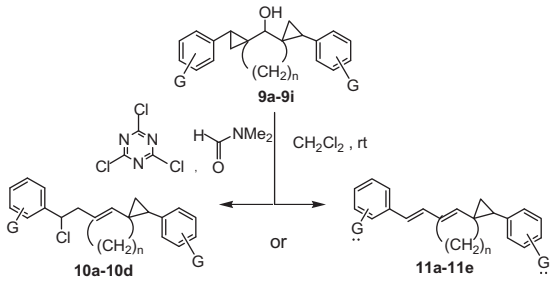


Figure 2. (a) Fluorescence spectrum of **8** and (b) UV spectra of A: **8** and B_1 to B_{14}: **8** after treatment with Fenton's reagent at 10 sec interval.



Scheme 4. Cleavage of bis-cyclopropylcarbinols.

expected to act as an efficient radical chain terminator. Such a compound **8**, which did not have any literature precedence, has been elegantly synthesized following the aforesaid protocol as delineated in Scheme 3. In general, TBDMS remains unaffected with TCT–DMF for phenol. But it is cleaved in the present system due to the higher nucleophilicity of Cl^- in aprotic nonpolar medium and greater nucleofugality of the resultant phenol **8** due to extended conjugation.

Compound **8** was strongly fluorescent at λ 403 nm with fluorescent intensity 250 a.u. (Fig. 2a).

Fenton's reaction[18a] is important in biology as it involves the creation of free radicals by chemicals present in vivo.[18b] Transition metal ions like iron and copper donate or accept free electrons via intracellular reactions and create free radicals promoting free radical damage.

Hydrogen peroxide is weakly active to initiate lipid peroxidation, but its activity as an 'active oxygen' species is profoundly increased due to the production of highly reactive hydroxyl radical through the Fenton's reaction which is responsible for oxidative damage to almost any biomolecule such as proteins, lipids and nucleic acid. So the reactivity of compound **8** was studied against Fenton's reagent mimicking the biological generation of radicals. The reaction was monitored with UV spectroscopy and the result is presented in Figure 2b. Compound **8** gave a strong UV absorption (A) at λ 348 nm (ε 7464) due to π–π^* transition which immediately disappeared after adding Fenton's reagent (B_1). This clearly indicates that compound **8** reacts instantly with Fenton's reagent and bears the promise of showing strong antioxidant activity against radical generating species analogous to biological system. It might have the potential to be used as a preventive for lipid peroxidation and preservation of fat molecules to increase their shelf lives.

As a continuation of the aforesaid investigations and to elaborate the synthetic potential of the present protocol, symmetrical bis-cyclopropylcarbinols (**9**) with differently substituted aryl moieties were reacted with TCT–DMF complex. One of the cyclopropane rings in **9** was selectively cleaved leaving behind the other intact (Scheme 4) and resulted in novel structural backbones with vinylcyclopropane motif. The products were either homoallylic chlorides (**10**) or dienes (**11**) depending on the electronic nature of the substituents (Table 2). Neither such cyclopropyl-substituted homoallylic chlorides (**10**) nor the cyclopropyl dienes (**11**) have any literature precedence till date to the best of our knowledge.

The presence of cyclopropane rings in **10** and **11** was confirmed from their ^1H and ^{13}C NMR spectra (See Supplementary material). The novel structural framework of these compounds was conclusively established by the single crystal X-ray diffraction study of **11d** (Fig. 3), where the simultaneous occurrence of the cyclopropane (C6–C7–C20) and the diene (C8–C11) moieties is clearly evident. Compounds **10b**, **10d**, **11b** and **11d** carried structurally important spiro [2.5]-oct-4-ene framework with immense possibility for further synthetic transformations leading to the

Table 2
Cleavage of bis-cyclopropylcarbinols **9** with TCT–DMF

Entry	*n*, G	Substrate (**9**)	Product (**10**/**11**)	Time (h)/yield[a] (%)
1	0, 4-Cl	**9a**	**10a**	12/86
2	3, 4-Cl	**9b**	**10b**	12/82
3	0, 4-Me	**9c**	**10c**	14/85
4	3, 4-Me	**9d**	**10d**	14/86
5	0, 4-OMe	**9e**	**11a**	15/82
6	3, 4-OMe	**9f**	**11b**	15/87
7	0, 3,4-$(OMe)_2$	**9g**	**11c**	15/86
8	3, 3,4-$(OMe)_2$	**9h**	**11d**	15/89
9	0, 3, 4(–OCH_2O–)	**9i**	**11e**	15/83

[a] Yield refers to isolated pure products fully characterized spectroscopically.

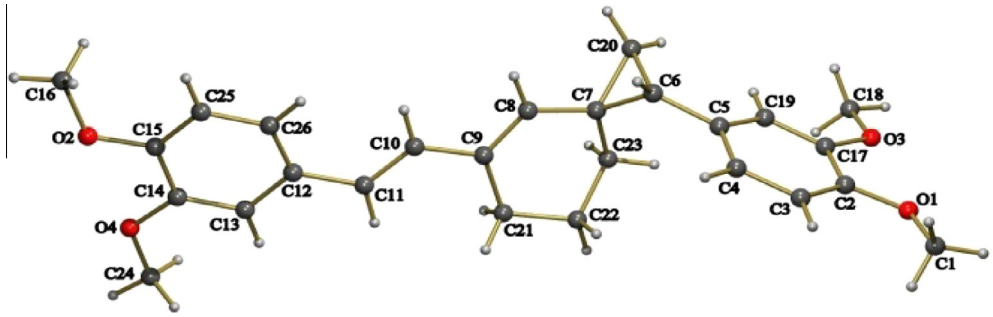


Figure 3. Ortep diagram of compound **11d**.[19]

construction of novel molecular backbones. Further transformations on the remaining cyclopropane motif do not occur under the present reaction condition owing to very mild electrophilic character of TCT–DMF adduct. So the present protocol provides a facile access to an unprecedented and structurally novel molecular framework with immense synthetic potential for future exploration.

An efficient and mild protocol for the synthesis of homoallylic chlorides and conjugated dienes of structural and functional importance has been developed utilizing the cleavage of appropriately substituted cyclopropylcarbinols using economically viable and easily accessible TCT–DMF adduct. One such newly synthesized phenolic diene described promising antioxidant activity. This method was elegantly extended towards the construction of novel and unprecedented molecular skeletons bearing cyclopropane ring having immense potential for further synthetic transformations through selective cleavage of symmetrical bis-cyclopropylcarbinols.

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Supplementary data

Supplementary data (general experimental procedure and the characterization data of the final compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.053.

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19. CCDC 990554 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).