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An unusual formation of diarylmethane scaffolds from 4-(halomethyl)cyclohex-2-enone derivatives

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ABSTRACT

A facile and efficient base promoted one-pot dimerization of halo cyclohexene derivatives leading to a de novo synthesis of biologically important diarylmethane and diarylmethanone derivatives is reported. A plausible mechanism for the unexpected formation of the title compounds involves dehydrohalogenation, 1,6-conjugate addition, subsequent aromatization through C–C bond cleavage and dehydrohalogenation.

Diarylmethane and diarylmethanone derivatives are one of the common structural motifs in natural products as well as some pharmaceutically important compounds.[1] Diarylmethane derivatives are used as PTP1B inhibitors,[2] chlorinated benzophenone antibiotics,[1c] antineoplastic agents,[1a] cytotoxic and antitubulin agents,[3] inhibition of respiratory complex II,[4] isocombretastatin A-4 analogs,[5] fluoro analogues of antimitotic phenstatin,[6] anticancer agents,[7] anti-HIV agents,[8] and non-nucleoside reverse transcriptase inhibitors.[9] Some of the biologically important diarylmethanone derivatives[1] are shown in Figure 1. Because of wide ranging applications of diarylmethane derivatives in medicinal chemistry, several methods have been reported for their syntheses. Some of the conventional methods for diarylmethanones include Friedel–Craft reactions,[10] usage of some of the oxidizing agents such as CrO_3–SiO_2,[11a] ^tBuOOH,[11b] SeO_2,[11c] and $KMnO_4$[11d] whereas diarylmethanes were obtained via reactions of organometallic reagents and transition-metal-catalyzed transformations.[12] However, newer methods leading to different substitution patterns with maneuverable groups are desirable in view of their biological significance.

Here we wish to report an unexpectedly observed dimerization reaction for the synthesis of diarylmethane derivatives through an interesting C–C bond cleavage under basic conditions at room temperature.

As a part of the exploration of chemistry of norbornyl α-diketones, we previously reported the Grob-fragmentation of α-diketones for the synthesis of six member α-ketoenols.[13] To further utilize this methodology we have chosen dione **1a** as a fragmentation precursor[14] to prepare the corresponding aromatic compound. Due to this, initially we subjected compound **1a** for Grob-fragmentation by treatment with *p*-toluenesulfonic acid monohydrate (PTSA) in refluxing toluene to obtain cyclohexenone **2a** in 90% yield.

Results obtained from optimization of fragmentation of compound **1a** with different acids and solvents are depicted in Table 1. It is clear that trifluoroacetic acid (TFA) in 1,2-DCE gave the best yield up to 99% under reflux condition. Additionally, the cyclohexenone derivatives **2b–d** were synthesized from **1b–d**, respectively (Scheme 1). Further, the compounds **2a–d** were treated with diazomethane in Et_2O/MeOH to afford the corresponding methylated products **3a–d**. Our initial goal was to convert the derivatives **3a–d** into the corresponding aromatic derivatives **3e** by dehydrohalogenation (Scheme 1). Treatment of **3a–d** with DBU in CH_2Cl_2 at 0 °C instead furnished dienones **4a–b** in excellent yields as summarized in Scheme 1.

We thought of attempting aromatization of **3a–d** by changing the solvent as well as the base employed. We chose K_2CO_3 in acetone for the purpose. Treatment of **3a** with K_2CO_3 in acetone at ambient temperature for 1 h also delivered dienone **4a** (94%). However, observation of a clean more polar product, which increased progressively with extended reaction time, prompted us to allow the reaction to proceed further at ambient temperature

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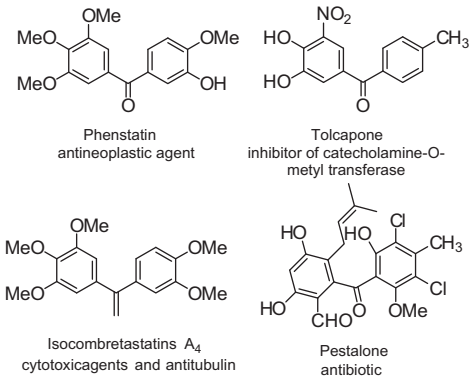


Figure 1. Biologically important diarylmethane motifs.

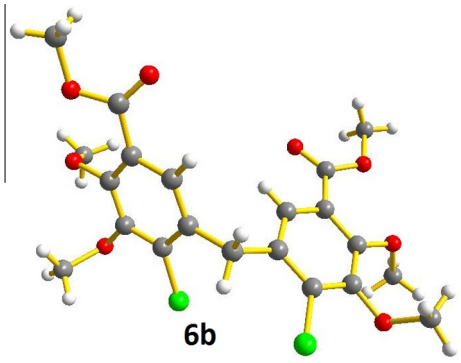
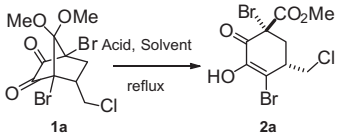


Figure 2. Molecular structure of **6b** as determined by X-ray crystallographic analysis.

Table 1
Optimization table for fragmentation reactions with different acids



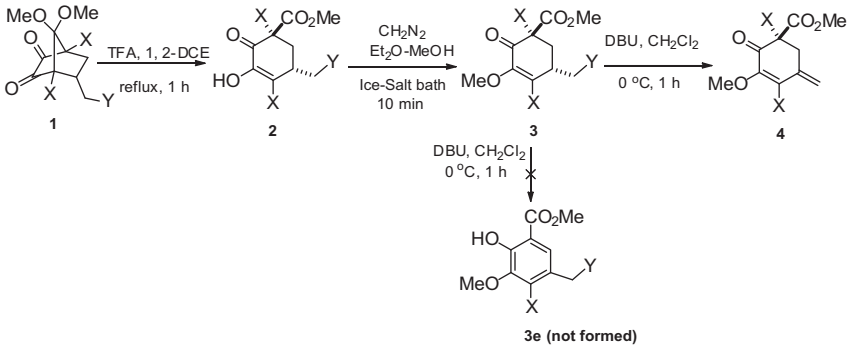
Entry	Acid	Solvent	Time (h)	Yield (%)
1	PTSA[a]	Toluene	4	90
2	TFA[b]	1,2-DCE	1	99
3	AcOH[c]	Benzene	7	91
4	10% HCl[c]	MeOH	6	92

[a] 4 equiv.
[b] 10 equiv.
[c] 2 mL per 1 mmol.

until the complete disappearance of the dienone **4a** (TLC monitoring). After allowing the reaction for 22 h, the new product formed was isolated in 85% yield. To our pleasant surprise, the new product turned out to be the diarylmethane derivative **5a** as evidenced from its spectral data. An unambiguous structural proof came from the single crystal X-ray analysis of **6b** (Fig. 2, vide infra). To explore this reaction further, other halocyclohexenone derivatives **3b**–**d** were treated with afore-mentioned conditions which gave the corresponding diarylmethane derivatives **5a** and **5b** (yield 81%). Because of potential biological importance of the diarylmethanone derivatives, we became interested in converting **5a**,**b** into the former via methylation of the phenol moiety followed by oxidation of the methylene group. Subjecting **5a**,**b** to MeI, K_2CO_3 in acetone afforded methylated products **6a**,**b** (97%, 98%) (see Scheme 2).

Oxidation of methylene groups in **6a**,**b** was achieved using CrO_3/Ac_2O to obtain diarylmethanone derivatives **7a**,**b** (84%, 80%). Further, we also converted ketone **7b** into olefin **8** by employing Wittig olefination with methyltriphenylphosphonium iodide/NaHMDS in THF at 0 °C (yield 90%). The reaction with **7a** did not proceed, perhaps due to steric hinderance caused by the bulky bromine atoms.

A plausible mechanism for the formation of diarylmethane derivative from **3** is depicted in Scheme 3. Initially, the treatment of compound **3** with K_2CO_3 would generate dienone **4** with exocyclic double bond via dehydrohalogenation. As dienone **4** has been isolated and well characterized, there is no ambiguity about its formation as an intermediate. A 1,6-conjugate addition of anion **A** or its resonance form, dienolate **B**, would result in intermediate '**C**'. The formation of anion **A** (or **B**) is possible either from **3** by direct proton abstraction by base or from **4** by 1,6-conjugate addition of the halide ion released in the first step. To account for the product formed, a C–C bond cleavage as depicted in Scheme 3, though speculative, is proposed leading to the intermediate **D**. Base mediated dehydrohalogenation (–HX) to gain aromaticity in



Entry	Substrate	X	Y	Products, isolated yields (%)		
				2	**3**	**4**
1	**1a**	Br	Cl	**2a**, 99	**3a**, 99	**4a**, 97
2	**1b**	Br	Br	**2b**, 99	**3b**, 99	**4a**, 96
3	**1c**	Cl	Cl	**2c**, 97	**3c**, 98	**4b**, 94
4	**1d**	Cl	Br	**2d**, 98	**3d**, 99	**4b**, 95

Scheme 1. Synthesis of cyclohexadienone **4** from norbornyl α-diketone **1**.