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The synthesis of phthalazin-1(2*H*)-ones and 3-hydroxyisobenzofuran-1(3*H*)-ones via the ring contraction of tropones

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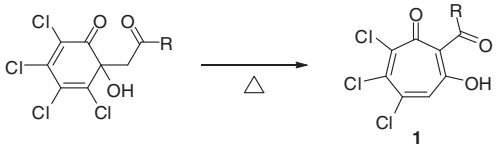
ABSTRACT

Phthalazin-1(2*H*)-ones and 3-hydroxyisobenzofuran-1(3*H*)-ones were synthesized by the reactions of tropones with hydrazines and alcohols, respectively, via the ring contraction.

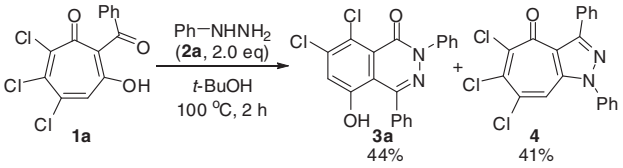
Cycloheptatrienone skeleton (tropone) is the key structural element in the troponoid family, which presents the interesting non-benzenoid aromatic structure.[1] Tropone derivatives are not only found in a wide range of biologically active natural products but are also useful building blocks in synthetic chemistry.[2] Therefore, the synthesis, structure, and reactivity of the troponoids have attracted considerable interest to organic chemists. Rather useful reactions of tropone nucleus are cycloaddition[3] and annulations,[4] providing accesses to functionalized bi- or multi-cyclic compounds. On the other hand, base-induced rearrangement of tropones to benzenoid compounds is also a well-known reaction pathway for tropone derivatives.[2] However, the formation of functionalized bicyclic products by the ring contraction of tropones has been virtually untouched.[5]

Recently, we developed an efficient ring expansion method for the synthesis of multiple functional tropone derivatives **1** (Eq. 1).[6] As the tropone **1** has three chloro-substituents, one active hydroxyl group and β-diketone structure, several interesting reactions were expected. Herein, we report our preliminary studies on the ring contraction of **1** introduced by hydrazines and alcohols.



(1)

Due to β-dicarbonyl structure of **1**, hydrazines **2** were initially used to evaluate the reactivity of **1**. Phthalazin-1(2*H*)-one **3a** was obtained unexpectedly together with an annulation product, pyrazol **4** (Eq. 2). Phthalazinones are biologically active compounds[7] and have attracted diverse areas of interests.[8] Several approaches have been reported for the synthesis of phthalazinones.[9] We envisioned that the present transformation could provide an alternative strategy to synthesize phthalazin-1(2*H*)-ones if the ring contraction occurred selectively.



(2)

A variety of hydrazines were tested to realize our hypothesis. Interestingly, the electron effect of hydrazines dramatically influenced the selectivity of the ring contraction of **1a**. Aromatic hydrazines **2** with electron-withdrawing group selectively afforded the ring-contraction products **3** (Table 1). 2,4-Dinitrophenyl hydrazine **2b** reacted with **1a** and gave the corresponding product **3b** in 94% yield (entry 1). Perfluorophenyl hydrazine **2c** also led to a good yield of the desired product **3c** (entry 2). A moderate yield of **3d** was obtained due to the formation of a **4**-type cycloaddition product in ca.6% yield (entry 3). Methyl-substituted tropone **1b** also selectively transformed into the corresponding ring-contraction products (entries 4 and 5). Although furan-substituted phthalazin-1(2*H*)-one **3g** was formed exclusively under the standard conditions, a slightly lower yield was attributed to a lower conversion of **1c** (entry 6).

A tentative mechanism for the formation of **3** is proposed (Scheme 1). The addition of **2** to **1** gives **A**, followed by the elimination of H_2O to afford **B**. We hypothesized that hydrazines **2** with an electron-withdrawing group would make this step feasible. Subsequently, intramolecular addition led to a five-membered intermediate **C**, followed by an electrocyclic reaction to give a tricyclic intermediate **D**. Finally, the three-membered ring opening generates the product **3**.

Interestingly, various alcohol **5** also induced the ring contraction of tropones **1b** to give 3-hydroxyisobenzofuran-1(3*H*)-ones **6** (Table 2). A 95% yield of **6a** was obtained when methanol **5a** was used as solvent (entry 1). The decreasing yields were observed when

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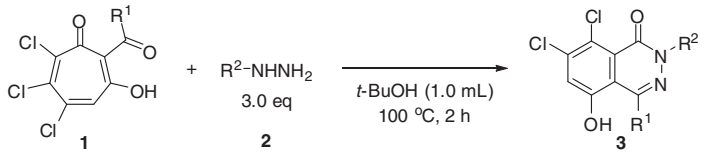
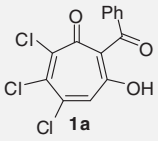
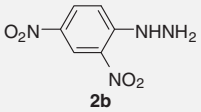
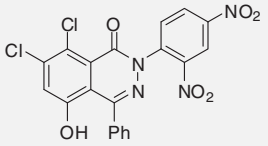
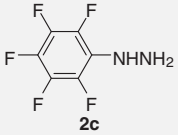
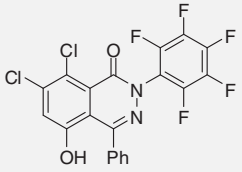
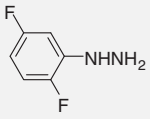
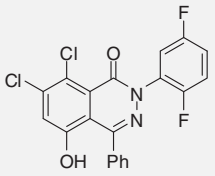
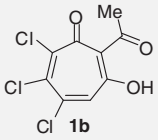
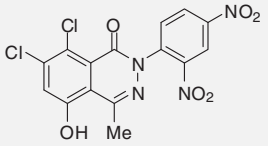
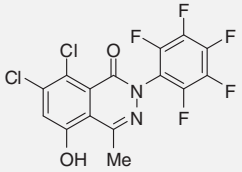
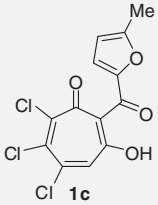
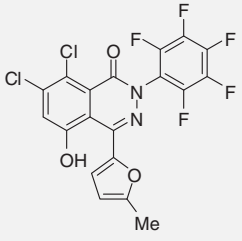
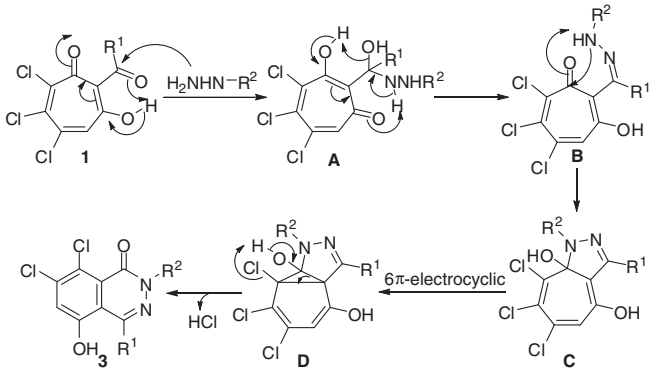
Table 1
The reactions of tropones **1** with hydrazines **2**[a]



Entry	1	2	3	Isolated yields (%)
1	 **1a**	 **2b**		**3b** 94
2	**1a**	 **2c**		**3c** 89
3	**1a**	 **2d**		**3d** 74
4	 **1b**	**2b**		**3e** 81
5	**1b**	**2c**		**3f** 86
6	 **1c**	**2c**		**3g** 68

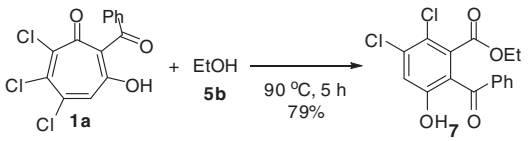
[a] Conditions: **1** (0.1 mmol), **2** (0.3 mmol); under nitrogen atmosphere.



Scheme 1. A tentative mechanism for the formation of **3**

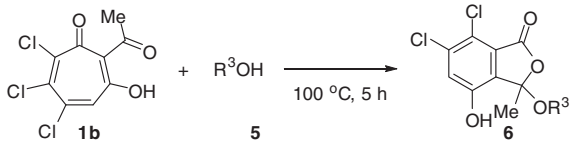
ethanol **5b** and *iso*-propanol **5c** were applied (entries 2 and 3). *tert*-Butyl alcohol **5d** does not induce the ring contraction (entry 4). Moreover, other alcohols **5e** and **5f** gave moderate yields of the corresponding products **6e** and **6f** (entries 5 and 6). Related to the hydrazine-induced ring contraction, we rationalized that the hemiketal intermediate **E** is generated firstly (Scheme 2). Keto-enol tautomerization gives the intermediate **F**. Oxygen instead of nitrogen attacks the carbonyl group of the tropone skeleton to generate a four-membered intermediate **G**, followed by the electrocyclic reaction and the three-membered ring opening to give the product **6**.

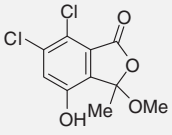
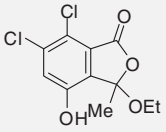
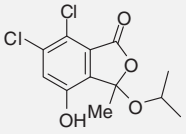
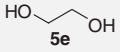
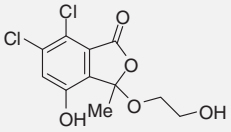
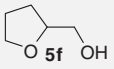
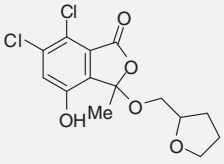
It should be noted that phenol derivative **7** instead of 3-hydroxyisobenzofuran-1(3*H*)-ones **6** was obtained when **1a** reacted with ethanol (Eq. 3). We hypothesized that a **6**-type intermediate was formed firstly in this reaction, followed by transesterification to give the ring-opening product **7**.



(3)

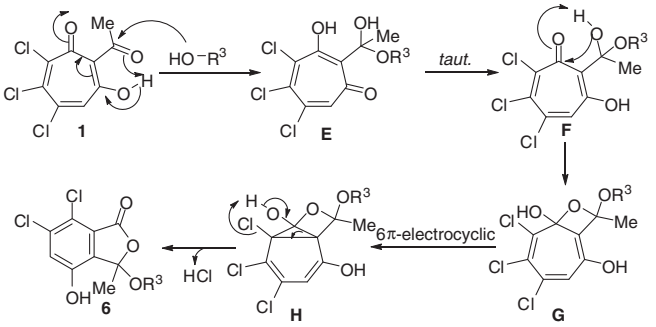
Table 2
The reactions of tropones **1b** with alcohols **5**[a]



Entry	6	7	Isolated yield (%)
1[b]	MeOH **5a**		**6a** 95
2[c]	EtOH **5b**		**6b** 85
3	 **5c**		**6c** 70
4	 **5d**	–	[d]
5	 **5e**		**6e** 68
6	 **5f**		**6f** 54

[a] Conditions: **1** (0.1 mmol), **5** (1.0 mL); under nitrogen atmosphere.
[b] 80 °C.
[c] 90 °C.
[d] No reaction.

In summary, we have reported a novel hydrazine-/alcohol-induced ring contraction of tropones, which provides a new protocol for the synthesis of the functionalized phthalazin-1(2*H*)-ones and 3-hydroxyisobenzofuran-1(3*H*)-ones. Further investigation of the reactivity of the multiple functional tropones **1** and the applications of phthalazinones **3** and isobenzofuranones **6** are in progress.



Scheme 2. A tentative mechanism for the formation of **6**

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.017.

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