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# Regio- and Diastereoselective Stepwise [8 + 3]-Cycloaddition Reaction between Tropone Derivatives and Donor–Acceptor Cyclopropanes

**Alexandra R. Rivero, Israel Fernández,* and Miguel Ángel Sierra***

*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, 28040-Madrid, Spain*

*israel@quim.ucm.es; sierraor@quim.ucm.es*

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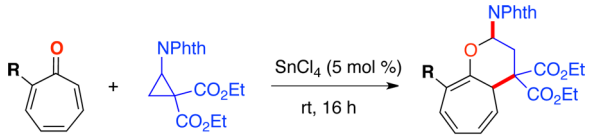
## ABSTRACT




**Regio- and diastereoselective stepwise [8+3]-cycloaddition**

**A novel $SnCl_4$-catalyzed [8 + 3]-cycloaddition reaction between tropone derivatives and donor–acceptor aminocyclopropanes is described. The process leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans with complete regio- and diastereoselectivity. Density functional theory calculations suggest that the cycloaddition occurs stepwise through an aromatic zwitterionic intermediate.**

Cycloaddition reactions are highly valuable transformations in modern organic synthesis because of their ability to increase the molecular complexity in a single synthetic step.[1] In this sense, donor–acceptor cyclopropanes (DACs),[2] which can be considered as 1,3-zwitterionic synthons, have proven to be very useful for the direct synthesis of five-membered carbo- and heterocycles via [3 + 2]-cycloaddition reactions.[3] Recent applications of these processes to the synthesis of complex natural products have clearly demonstrated their potential in organic synthesis.[4] Nevertheless, the use of DACs in high-order cycloaddition reactions has been scarcely explored.[5]

Within the context of our ongoing work in the reaction mechanims and synthetic applications of cycloaddition reactions[6] and based on previous studies,[7] we recently reported that tropone derivatives can be used as 8-component

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(7) For a review on high-order cycloadditions involving tropone derivatives, see: (a) Nair, V.; Abhilash, K. G. *Top. Heterocycl. Chem.* **2008**, *13*, 173. (b) Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino, A. L.; Tomás, M. *Chem.—Eur. J.* **2009**, *15*, 8800.

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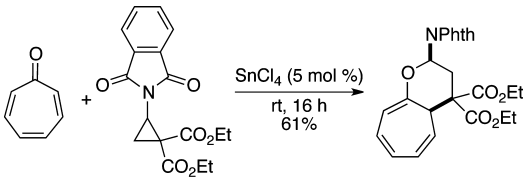
in high-order [8 + 2]-cycloaddition reactions.[8] These previous results prompted us to explore the reaction between DACs and tropone derivatives, which would lead to the formation of [8 + 3]-cycloadducts. In addition, Density Functional Theory (DFT) calculations were carried out to unravel the reaction mechanism of this novel transformation.

The reaction between the parent tropone **1a** and donor−acceptor aminocyclopropane **2** was explored first. This particular DAC was chosen due to its proven ability to produce *N*-containing hetero- and carbocycles as recently demostrated by Waser and co-workers.[9] Optimization of the reactions conditions (different Lewis acids, temperature, solvent, and stoichiometry) indicated that the use catalytic amounts of $SnCl_4$ (5 mol %) and equimolar amounts of **1a** and **2**, in $CH_2Cl_2$ as solvent, at room temperature leads to the formation of cycloaduct **3a** in 61% reaction yield (Scheme 1).[10] Interestingly, no traces of the corresponding [3 + 2]-cycloadduct (the product observed in the related reaction involving different ketones and **2**)[9c] were detected in the crude reaction mixtures. The bias of tropone to experience high order cycloaddition reactions can be ascribed to its peculiar electronic structure (see below).[7,8] In addition, **3a** is formed exclusively as the *syn* diastereoisomer as revealed by NOESY experiments. Therefore, this novel [8 + 3]-cycloaddition reaction involving **1a** occurs with complete diastereoselectivity.[11]

To gain more insight into the origin of the diastereoselectivity of the above process, a computational DFT study was carried out.[12] The computed reaction profile of the process between **1a** and **2** is illustrated in Figure 1, which shows the relative free energies in $CH_2Cl_2$ solution.

As proposed previously,[13,14] the process is assumed to begin with the coordination of the Lewis acid to the DAC to produce the intimate ion pair **4a**, which is in equilibrium with the completely dissociated zwitterion **4b**. Nucleophilic attack of the lone pair of the oxygen atom of **1a** to the iminium cation moiety of **4b** leads to the formation of the zwitterionic intermediate **INT1**. The ease of this process, which occurs via transition state **TS1**, is reflected in the very low activation barrier ($\Delta G_{a,298}$ = 2.8 kcal/mol) and exergonicity ($\Delta G_R$ = −3.1 kcal/mol) computed for this transformation. From **INT1**, a ring closure reaction occurs to produce the corresponding [8 + 3]-cycloadduct **INT2** via **TS2**, a saddle point associated with the formation of the new C−C bond (see optimized geometries of **TS2** in the Supporting Information).

**Scheme 1.** [8 + 3]-Cycloaddition between Tropone **1a** and **2**



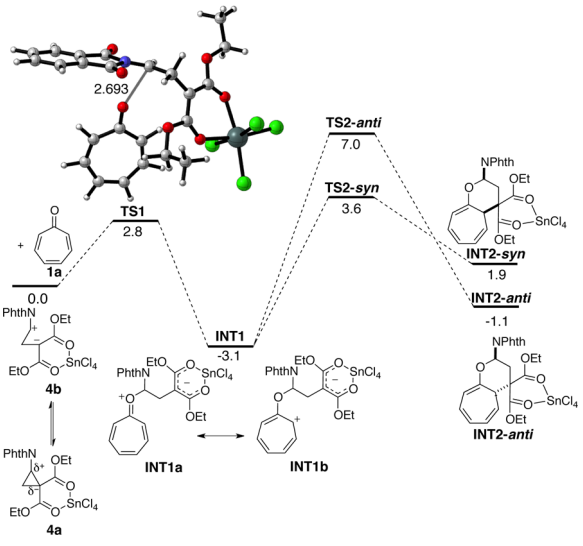




**Figure 1.** Computed reaction profile of the [8 + 3]-cycloaddition between tropone **1a** and $SnCl_4$−DAC complex **4**. Relative free energies ($\Delta G$, 298 K) and bond distances are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM($CH_2Cl_2$)-B3LYP/def2-SVP level.

Two possible ring closures leading to the *syn*- and *anti*-cycloadducts are possible. As readily seen in Figure 1, the experimentally observed exclusive formation of the *syn*-isomer takes place under kinetic control in view of the lower activation barrier computed for the process involving the saddle point **TS2-*syn*** ($\Delta\Delta G_a$(*syn*-*anti*) = 3.4 kcal/mol). Final decoordination of $SnCl_4$ in **INT2-*syn*** produces the observed [8 + 3]-cycloadduct **3a** thus regenerating the catalyst. Therefore, similar to related high-order cycloaddition reactions involving tropone derivatives,[8] the present [8 + 3]-cycloaddition between the parent tropone **1a** and DAC **2** occurs stepwise through a zwitterionic intermediate (**INT1**).

(8) (a) Lage, M. L.; Fernández, I.; Sierra, M. A.; Torres, M. R. *Org. Lett.* **2011**, *13*, 2892. (b) Rivero, A. R.; Fernández, I.; Sierra, M. A. *J. Org. Chem.* **2012**, *77*, 6648.

(9) (a) de Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. (b) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386. (c) Benfatti, F.; de Nanteuil, F.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 4844.

(10) Typical procedure: In a two-necked flask equipped with a nitrogen inlet, tropone **1a** (1 equiv) and aminocyclopropane **2** (1 equiv) were dissolved in anhydrous dichloromethane at room temperature. After 5 min, $SnCl_4$ in dichloromethane (5 mol %) was added. The mixture was stirred under nitrogen at 16 h, and then the reaction was quenched by the addition of triethylamine and subsequently flushed through a short plug of silica gel, eluting with EtOAc. The solvent was removed in vacuo to give the crude reaction mixture, which was submitted to flash column chromatography to yield pure cycloadduct **3a**.

(11) The reaction between diethyl 2-phenylcyclopropane-1,1-dicarboxylate and tropone **1a** was also tested. Under the same reaction conditions used for the aminocyclopropane **2** (i.e., 5 mol % $SnCl_4$, rt, 16 h), the corresponding [8 + 3]-cycloadduct was not formed.

(12) DFT calculations were carried out at the PCM($CH_2Cl_2$)-B3LYP/def2-SVP level of theory using the Gaussian 09 suite of programs. See computational details in the Supporting Information.

(13) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

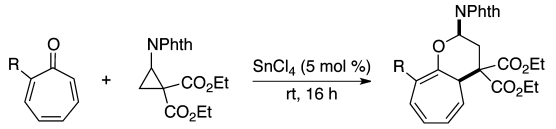
(14) For a computational study on the Sn(II)-catalyzed [3 + 2]-cycloaddition reaction between DACs and benzaldehyde, see: Zhang, J.; Shen, W.; Li, M. *Eur. J. Org. Chem.* **2007**, 4855.

The structure of zwitterion **INT1** deserves further analysis. As shown in Figure 1, **INT1** can also be described by the resonance form **INT1b**, where the positive charge is delocalized within the seven-membered ring. This species, which resembles the tropyl cation, should therefore possess remarkable aromatic character. Indeed, the computed negative Nucleus Independent Chemical Shift (NICS)[15] values (NICS(0) = −3.6 and NICS(1) = −7.2 ppm) and the corresponding out-of-plane tensor component ($NICS(1)_{zz}$ = −16.7 ppm) confirm the magnetic aromatic nature of this zwitterion. In addition, the optimized geometry of **INT1** indicates that the seven-membered ring is highly planar (C1(O)−C2−C3−C4 dihedral angle of −0.3°) with C−C bond distances which are intermediate between single and double bonds (ranging from 1.382 to 1.425 Å), thus satisfying the so-called geometrical criterion for aromaticity as well.[16] Therefore, it can be suggested that the gain in stability by aromaticity occurring in **INT1** is in part responsible for the stepwise nature of the transformation.

Once the reaction mechanism of the process was analyzed, the influence of substituents attached to the tropone ring on the regioselectivity of the [8 + 3]-cycloaddition was explored. To this end, a series of different 2-substituted tropones **1b**−**j** having donor or acceptor groups directly attached to the C2-carbon atom of the tropone ring were reacted with DAC **2** in the reaction conditions used above (i.e., 5 mol % $SnCl_4$, room temperature, $CH_2Cl_2$ for 16 h). As shown in Scheme 2, all the reactions tested lead to the formation of the corresponding [8 + 3]-cycloadducts **3** in good yields, with the exception of the reactions involving 2-alkoxytropones **1i** and **1h** and 2-silyloxytropone **1j**, which were recovered unaltered together with a new product arising from the cyclopropane (see below). Strikingly, in all cases the ring closure occurred at the C7-carbon atom of the initial tropone, which indicates that this [8 + 3]-cycloaddition reaction proceeds with complete regioselectivity (no traces of the corresponding C2-cycloadduct were observed in the respective reaction crudes). In addition, and as expected, cycloadducts **3b**−**g** were formed exclusively as *syn*-diastereoisomers as confirmed by NOESY experiments. Single crystals of the cycloadduct **3e** (grown in hexanes/$CH_2Cl_2$ solution) suitable for X-ray diffraction analysis fully confirm, by analogy, both the regio- and the relative stereochemistry of compounds **3** (Figure 2).

We carried out DFT-calculations as well to understand the regioselectivity, namely the exclusive formation of the C7- over the C2-cycloadduct, of the transformation. Thus, both regioisomeric *syn*-ring closure reactions arising from the zwitterionic species **INT1-Ph2** and **INT1-Ph7**, formed upon the initial nucleophilic attack of the phenyltropone **1d** to **4b**, were computed. As readily seen in Figure 3, the ring closure leading to the C7-regioisomer (via **TS2-Ph7**) is kinetically ($\Delta\Delta G_a$(Ph7−Ph2) = 14.4 kcal/mol) and also

**Scheme 2.** [8 + 3]-Cycloaddition Reactions between 2-Substituted Tropones **1b**−**j** and **2**




**1b**, R = Cl
**1c**, R = Br
**1d**, R = Ph
**1e**, R = 4-Me-$C_6H_4$
**1f**, R = 4-OMe-$C_6H_4$
**1g**, R = 4-$NO_2$-$C_6H_4$
**1h**, R = OMe
**1i**, R = OBn
**1j**, R = OTBS

**2**

**3b**, R = Cl (68%)
**3c**, R = Br (64%)
**3d**, R = Ph (68%)
**3e**, R = 4-Me-$C_6H_4$ (65%)
**3f**, R = 4-OMe-$C_6H_4$ (62%)
**3g**, R = 4-$NO_2$-$C_6H_4$ (71%)
**3h**, R = OMe (0%)[a]
**3i**, R = OBn (0%)[a]
**3j**, R = OTBS (0%)[a]

[a] No cycloadduct was formed. See text.

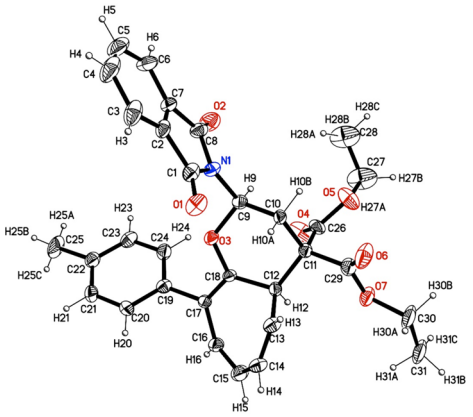


**Figure 2.** ORTEP-diagram of compound **3e**. Ellipsoids are drawn at the 30% probability level.

thermodynamically ($\Delta\Delta G_R$(Ph7−Ph2) = 12.9 kcal/mol) favored over the ring closure process forming the C2-regioisomer via **TS2-Ph2**. A similar result was computed in the [8 + 3]-cycloaddition involving 2-bromotropone **1c** ($\Delta\Delta G_a$(Br7−Br2) = 6.8 kcal/mol). As the electronic effects of phenyl and bromide substituents are markedly different, and no effect of the substituents attached to the aromatic ring was observed, this regioselectivity should be steric in origin. It can be thus suggested that the steric hindrance exerted by the substituent attached at the C2-position may hamper the ring closure at this position directing the ring closure to occur at the sterically unhindered C7-position of the tropone ring.

As stated above, 2-alkoxytropones **1h** and **1i** and 2-silyloxytropone **1j** did not undergo the [8 + 3]-cycloaddition, which may be attributed to the electronic effect exerted by the donor alkoxy or silyloxy group.[17] Instead, a new

(15) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842.
(16) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *68*, 209 and references therein.
(17) Alternatively, coordination of the 2-alkoxytropone to the catalyst may be responsible for the lack of reactivity of compounds **1h** and **1i**. However, this coordination seems unlikely in the presence of the bulky TBS-substituent of compound **1j**. We thank a reviewer for pointing out this experiment.

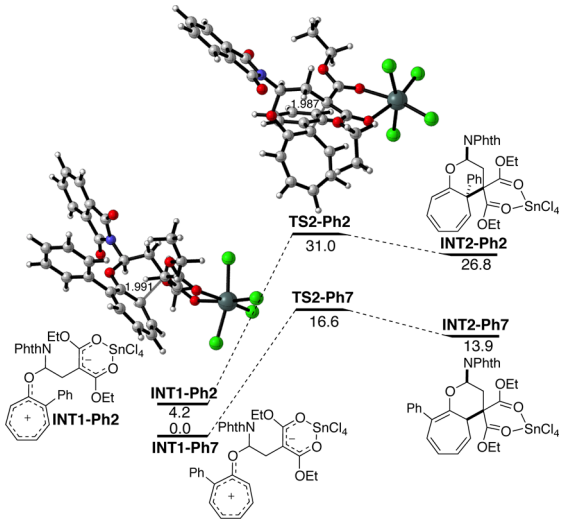



**Figure 3.** Computed profile for the ring closure of the [8 + 3]-cycloaddition between tropone **1d** and $SnCl_4$–DCA complex **4**. See caption for Figure 1 for additional details.

compound **5** lacking the characteristic signals of the tropone in the corresponding NMR spectra was isolated in the processes involving **1h** and **1i**. Single crystals of the new compound **5** suitable for X-ray diffraction analysis were grown in hexanes/$CH_2Cl_2$ solution at room temperature. As seen in Figure 4, the structure of **5** corresponds to a dimer of the DAC **2**. As tropones **1h,i** were recovered unaltered in the reaction conditions used,[18] species **5** is very likely formed by the self-coupling of two molecules of the $SnCl_4$–DAC complex **4**. The formation of this dimer constitutes therefore a side reaction which occurs when DAC **2** reacts with electron-rich substrates such as alkoxytropones. We want to point out that, although the self-dimerization product of **2** has not been observed so far,[9] related dimerization products of DACs have been described.[19]

In summary, the novel Lewis acid catalyzed [8 + 3]-cycloaddition reaction between tropone and tropone

(18) Moreover, dimer **5** was formed in the reactions of tropones **1h,i** with **2** at −78 °C for prolonged reaction times. In addition, in a control experiment, dimer **5** was also formed in the reaction of DAC **2** and $SnCl_4$ conducted in the absence of any tropone derivative.

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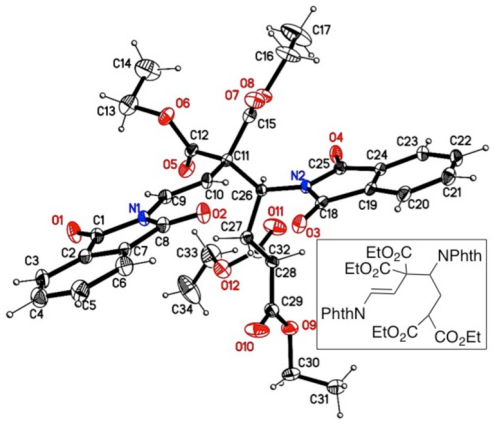


**Figure 4.** ORTEP-diagram of compound **5**. Ellipsoids are drawn at the 30% probability level.

derivatives and donor–acceptor aminocyclopropane **2** has been studied. The process leads to the formation of amino-substituted tetrahydrocyclohepta[*b*]pyrans in good reaction yields and with complete regio- and diastereoselectivities. By means of computational-DFT methods, it was found that this transformation proceeds stepwise through a zwitterionic intermediate, which resembles the tropyl cation and therefore is stabilized by some degree of $\pi$-aromaticity. From this intermediate, a ring closure step, which controls the regio- and diastereoselectivities, occurs to produce the observed [8 + 3]-cycloadducts.

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**Supporting Information Available.** Experimental details, NMR spectra of isolated compounds, crystallographic data for compounds **3e** and **5**, computational details, Cartesian coordinates, and free energies of all the stationary points discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.