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Electronic-State Switching Strategy in the Photochemical Synthesis of Indanones from *o*-Methyl Phenacyl Epoxides

Peter Štacko,[†] Tomáš Šolomek,*[,†,‡] and Petr Klán*[,†,‡]

Department of Chemistry, Faculty of Science, Masaryk University, Kamenice 5/A8, 625 00 Brno, Czech Republic, and Research Centre for Toxic Compounds in the Environment, Faculty of Science, Masaryk University, Kamenice 3, 625 00 Brno, Czech Republic

tom.solomek@gmail.com, klan@sci.muni.cz

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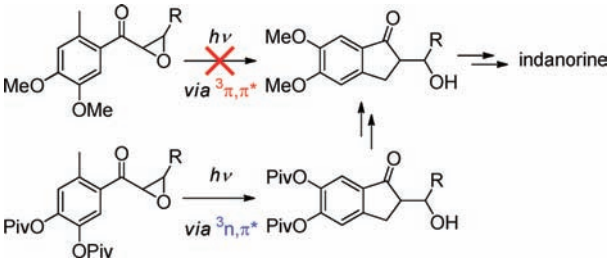
ABSTRACT



An electronic excited-state switching strategy has been utilized to control the selectivity of a key photochemical step in the total synthesis of indanorine. The excited-state character of 4,5-dimethoxy-2-methylphenacyl epoxide was changed from an unfavorable $^3\pi,\pi^*$ state to a productive $^3n,\pi^*$ state by a temporary structural modification, resulting in a relatively efficient and high-yielding formation of an indanone derivative. The corresponding structural modification was selected on the basis of quantum chemical calculations prior to the synthesis.

In the past decades, several strategies have been developed to efficiently control the chemo- or regioselectivity of organic reactions. In photochemical reactions, selectivity remains to be a challenging task in targeted synthesis.[1] Complicating features of excited state reactions, such as close-lying electronic states, conical intersections, or small reaction barriers, hamper the predictability of photochemical reactions. For example, the chemical reactivity of two close-lying triplet electronic states of phenyl ketones, the relative energies of which are strongly influenced by substitution on the aromatic ring or by the solvent, is known to differ markedly.[2] Hence, classical free energy relationships often fail to predict excited state behavior.[2c,d,3]

The order of the triplet energy levels is decisive for reactions involving an excited-state hydrogen-atom transfer step, such as the photoenolization of substituted *o*-methylphenyl ketones **1** (Scheme 1).[1,2e,2f,4] Hydroxy-*o*-quinodimethane intermediates (*o*-xylylenols, **2**) thereby photogenerated have been used in the synthesis of various pharmaceutically relevant compounds possessing an indanone core (**3**, in red; Scheme 1), such as donepezil hydrochloride[5] or pterosines,[6] from **1** when good leaving groups (X = LG) were present in an appropriate position. These reactive intermediates can also be trapped in situ in a

[†] Department of Chemistry.
[‡] Research Centre for Toxic Compounds in the Environment.

(1) Klan, P.; Wirz, J. *Photochemistry of Organic Compounds: From Concepts to Practice*; Wiley: Chichester, U. K., 2009.
(2) (a) Li, Y. H.; Lim, E. C. *Chem. Phys. Lett.* **1970**, *7*, 15–18. (b) Rauh, R. D.; Leermakers, P. A. *J. Am. Chem. Soc.* **1968**, *90*, 2246–2249. (c) Wagner, P. J.; Kemppainen, A. E.; Schott, H. N. *J. Am. Chem. Soc.* **1973**, *95*, 5604–5614. (d) Wagner, P. J.; Siebert, E. J. *J. Am. Chem. Soc.* **1981**, *103*, 7329–7335. (e) Wagner, P. J.; Klan, P. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W. M., Lenci, F., Eds.; CRC Press LLC: Boca Raton, FL, 2003; Chapter 52, pp 1−31. (f) Solomek, T.; Stacko, P.; Veetil, A. T.; Pospisil, T.; Klan, P. *J. Org. Chem.* **2010**, *75*, 7300–7309. (g) Sebej, P.; Lim, B. H.; Park, B. S.; Givens, R. S.; Klan, P. *Org. Lett.* **2011**, *13*, 644–647.
(3) Loutfy, R. O. *Tetrahedron* **1973**, *29*, 2251–2252.
(4) (a) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595–2607. (b) Pelliccioli, A. P.; Klan, P.; Zabadal, M.; Wirz, J. *J. Am. Chem. Soc.* **2001**, *123*, 7931–7932. (c) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405.
(5) Pospisil, T.; Veetil, A. T.; Lovely Angel, P. A.; Klan, P. *Photochem. Photobiol. Sci.* **2008**, *7*, 625–632.
(6) (a) Wessig, P.; Glombitza, C.; Muller, G.; Teubner, J. *J. Org. Chem.* **2004**, *69*, 7582–7591. (b) Wessig, P.; Teubner, J. *Synlett* **2006**, 1543–1546.
(7) (a) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3679–3683. (b) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675–3678. (c) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 613–627.

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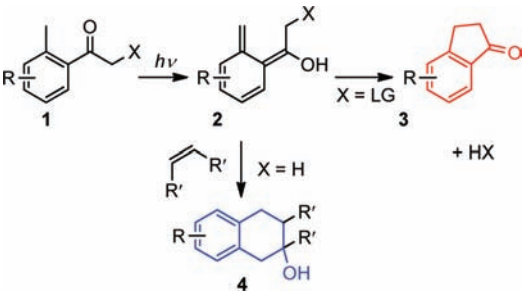
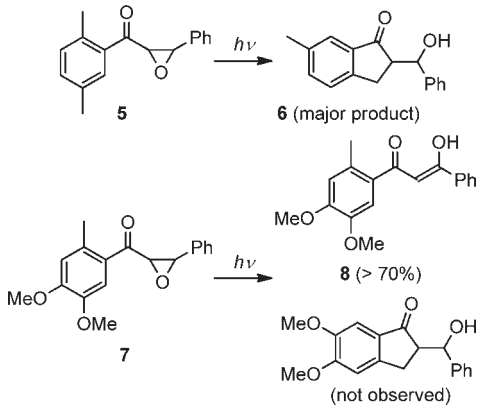
Scheme 1. Synthetic Applications of Photoenolization



stereospecific [4 + 2] (Diels–Alder) cycloaddition reaction to construct benzannulated polycyclic systems (**4**, in blue; Scheme 1), for example, in the total synthesis of hamigerans.[7]

Scheme 2. Photoreactions of *o*-Methylphenacyl Epoxides[2f]

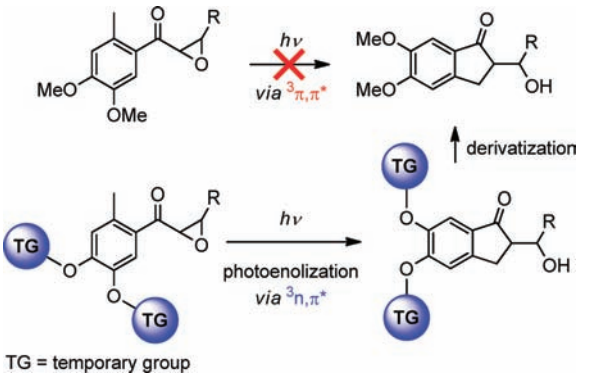


Recently, we have introduced a novel cyclization reaction based on the photoenolization of *o*-methylphenacyl epoxides (**5** and **7**, Scheme 2).[2f] In one case (**5**), formation of hydroxy-*o*-quinodimethanes via the ^{3}n,π^* state led to subsequent oxiranyl ring-opening and cyclization to give the β-hydroxy indanone **6**, analogous to the family of pterosines.[8] However, two electron-donating methoxy substituents, attached to the phenyl ring of many interesting indanone derivatives,[9] completely altered the selectivity of the photoreaction by inverting the triplet-state energies of the parent phenyl ketone (**7**): a homolytic C–O cleavage, originating from the $^3\pi,\pi^*$ state, resulted in production of the 3-hydroxypropenone **8**.[2f]

(8) Kobayashi, A.; Egawa, H.; Koshimizu, K.; Mitsui, T. *Agric. Biol. Chem.* **1975**, *39*, 1851–1856.

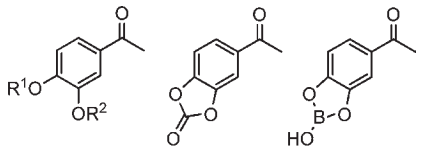
(9) (a) Hua, X. Q. H.; Genini, D.; Gussio, R.; Tawatao, R.; Shih, H.; Kipps, T. J.; Carson, D. A.; Leoni, L. M. *Cancer Res.* **2001**, *61*, 7248–7254. (b) Shih, H. C.; Deng, L.; Carrera, C. J.; Adachi, S.; Cottam, H. B.; Carson, D. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 487–490. (c) Mohapatra, P. P.; Laxminarayan, B. WO/2008/073452, 2008. (d) Sugimoto, H.; Iimura, Y.; Yamanishi, Y.; Yamatsu, K. *J. Med. Chem.* **1995**, *38*, 4821–4829. (e) Rizzo, S.; Bartolini, M.; Ceccarini, L.; Piazzi, L.; Gobbi, S.; Cavalli, A.; Recanatini, M.; Andrisano, V.; Rampa, A. *Bioorg. Med. Chem.* **2010**, *18*, 1749–1760. (f) Li, M. Y.; Xia, L. *Chem. Biol. Drug Des.* **2007**, *70*, 461–464.

Scheme 3. Electronic-State Switching Strategy



We now expand the scope of the synthesis of pharmaceutically promising indanones using a key photochemical step by introducing an excited-state switching strategy as demonstrated in Scheme 3. The idea was to deliberately control the selectivity of a photoreaction by the introduction of temporary "dummy" group(s), with the intent to facilitate the desired transformation. A suitable group was chosen from a small library generated by simple DFT-based quantum chemical calculations to avoid excessive laboratory experiments. Subsequently, the selected substrate was synthesized and utilized in the total synthesis of indanorine, an antiproliferative agent,[9b] structurally analogous to indanocine.[9a,10] To the best of our knowledge, such a rational approach in organic synthesis involving a photochemical step is unprecedented.

Table 1. Lowest Triplet State Configurations of **9a**–**d**



	lowest triplet state[a]	
compound	gas phase	PCM[b]
9a	π,π^*	π,π^*
9b	n,π^*	π,π^*
9c	n,π^*	π,π^*
9d	n,π^*	n,π^*

[a] The character of the lowest triplet DFT wavefunction calculated at the UB3LYP/6-31+G* level of theory. [b] Acetonitrile used as a polarizable continuum (PCM, ε_r = 35.688).

Computational Selection of the Temporary Group. The library of candidates consists of simple acetophenones

(10) Leoni, L. M.; Hamel, E.; Genini, D.; Shih, H. C.; Carrera, C. J.; Cottam, H. B.; Carson, D. A. *J. Natl. Cancer Inst.* **2000**, *92*, 217–224.

9a–**d** substituted by common protecting groups often used in the chemistry of catechol (Table 1). The nature of the triplet-state wavefunctions in **9a**–**d** was evaluated by inspection of their singly occupied molecular orbitals (SOMOs) at their minimum triplet energy geometries in both the gas phase and a polarizable continuum (PCM) to mimic the solvation effects. We relied on the fact that the solution of SCF equations converges to the lowest energy state in a given irreducible representation of a symmetry point group.[11] Hence, we forced the structures to retain C_1 symmetry, where both the ^{3}n,π^* and $^3\pi,\pi^*$ states belong to the same irreducible representation (see the Supporting Information for more details). While the lowest triplet state was predicted to have a $^3\pi,\pi^*$ configuration in polar acetonitrile in the case of **9a**–**c**, the acyl groups in **9d** preserved the ^{3}n,π^* configuration in both media (Figure 1). Both acyl groups in **9d** are twisted out of the benzene ring plane, thereby reducing the stabilizing conjugation that favors the $^3\pi,\pi^*$ state.[2c–e] We should note here that DFT methods generally overestimate the stability of the ^{3}n,π^* states in ketones, whereas they describe the $^3\pi,\pi^*$ states more accurately.[12] Nevertheless, the character of the lowest triplet state found for **9d** suggests that both states should, at least, be close enough in energy to enable efficient hydrogen-atom transfer.[13]

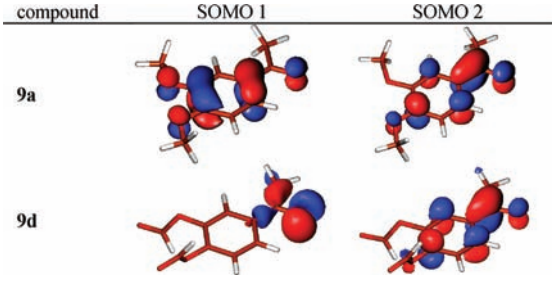
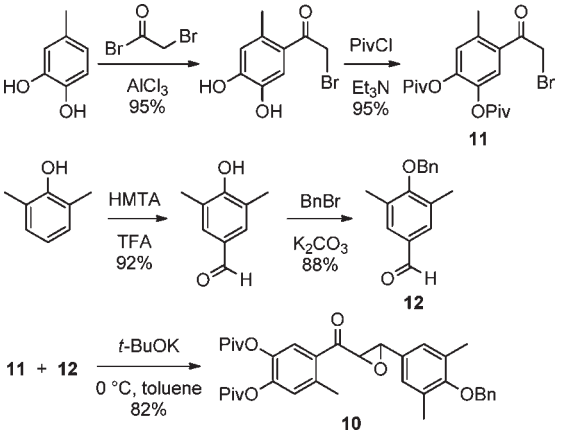


Figure 1. Singly occupied molecular orbitals (SOMOs) of **9a** ($^3\pi,\pi^*$) and **9d** (^{3}n,π^*).

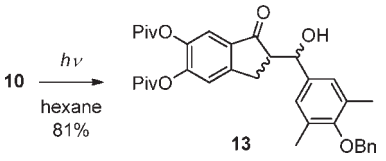
Synthesis. The pivaloyl group was chosen as a temporary group because of its bulkiness, immediate synthetic availability, and relative chemical stability even under basic conditions, which we required for indanorine synthesis later. The starting epoxy ketone **10** was synthesized via the Darzens condensation protocol from the acetophenone **11** and the benzaldehyde **12** (Scheme 4). The former compound was prepared by a Friedel–Crafts acylation of 4-methylcatechol with bromoacetyl bromide and subsequent reaction with pivaloyl chloride in excellent yields. The latter one was synthesized by a Duff formylation of

Scheme 4. Synthesis of the Epoxide **10**



2,6-xylenol by HMTA in trifuoroacetic acid,[14] followed by protection of the free hydroxyl group with benzyl bromide in 81% overall yield. The condensation of **11** and **12** in the presence of LDA in THF at −78 °C gave **10** in 35% yield. KHMDS as a base improved the yield only moderately (to 45%); the long reaction time required under these conditions was accompanied by unwanted side-reactions. This was circumvented by carrying out the condensation with potassium *t*-butoxide in dry toluene. The reaction provided **10** exclusively as a *trans* diastereomer in 82% yield at 0 °C within 1 h. Note that the reaction is extremely sensitive to residual water, which causes a detrimental decrease of the chemical yield.

Scheme 5. Formation of the Indanone **13** from **10**



Photochemistry. Subsequent irradiation of a deoxygenated solution of **10** ($c = 3 \times 10^{-3}$ M) in hexane with a medium-pressure mercury lamp through a Pyrex filter ($\lambda > 290$ nm) led to the formation of a mixture of the indanone diastereomers **13** (Scheme 5) in a ratio of approximately 1:1 (NMR, HPLC). **13** was essentially the sole photoproduct observed. An undesired product analogous to the 3-hydroxypropenone **8** (Scheme 2), the formation of which would indicate that the reaction

(11) Note: In our case, the system of the two triplet states can be well described by single determinantal methods, such as DFT, as evidenced by preliminary CASSCF calculations.

(12) Muthukrishnan, S.; Mandel, S. M.; Hackett, J. C.; Singh, P. N. D.; Hadad, C. M.; Krause, J. A.; Gudmundsdottir, A. D. *J. Org. Chem.* **2007**, *72*, 2757–2768.

(13) Encina, M. V.; Lissi, E. A.; Lemp, E.; Zanocco, A.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 1856–1860.

(14) Smith, W. E. *J. Org. Chem.* **1972**, *37*, 3972–3973.

(15) (a) dos Santos, F. R.; da Silva, M. T.; Netto-Ferreira, J. C.; de Lucas, N. C. *Quim. Nova* **2007**, *30*, 897–900. (b) Note: In fact, the indanone **13** is poorly soluble in hexane and precipitates at the concentrations used, which may considerably decrease the efficiency of unwanted secondary photoreactions. Moreover, the yield of **13** formation could be, in principle, improved by setting the irradiation wavelength to approximately 266 nm, where the ratio of the absorption coefficients of **10** and **13** reaches its maximum (see Figures S24 and S25 in the Supporting Information).

proceeded via a $^3\pi,\pi^*$ state and homolytic C−O bond cleavage, was not detected. Elevated temperatures (>40 °C) were avoided during the manipulation to prevent a retro-aldol reaction. The maximum chemical yield (93%, HPLC; 81%, isolated) was obtained at 85% conversion of **10** (10% of unreacted starting material was recovered). At higher conversions, the yield began to decrease because of secondary photoreactions, as has been observed in the photochemistry of other phenyl ketone derivatives.[2f,15]

The quantum yields (Φ) of **13** formation are summarized in Table 2. The value in dry acetonitrile, which compares well to that previously reported for 2,5-dimethylbenzoyl oxiranes,[2f] was half of that found in hexane. The quantum yield changed only a little when wet acetonitrile was used.

Table 2. Quantum Yields (Φ) of **13** Formation

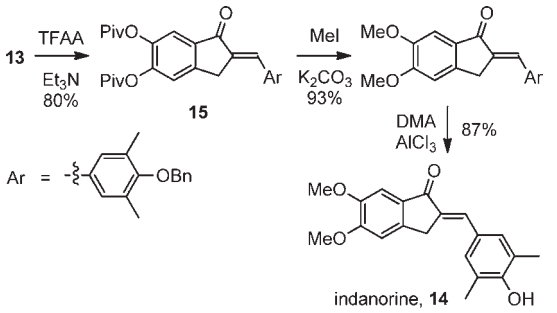
solvent	Φ^a
hexane	0.49 ± 0.01
dry acetonitrile	0.22 ± 0.01

[a] Degassed solutions (~5×10^{-4} M) in acetonitrile or hexane were irradiated at $\lambda = 313$ (±5 nm) on an optical bench. Φ was determined using valerophenone as an actinometer (Φ of acetophenone formation is 0.33 in hexane).[16] The results are based on at least five independent measurements (HPLC); the standard deviations of the mean are shown.

Indanorine Synthesis. Finally, a practical application of our electronic-state switching strategy is demonstrated on the total synthesis of the antiproliferative agent indanorine **14** (Scheme 6). Unlike our previous work,[2f] where dehydration of β-hydroxy indanone was carried out using methanolic KOH at elevated temperatures, all our attempts to treat **13** with a catalytic amount of an acid or base at ambient or elevated temperatures resulted in its prompt decomposition to retro-aldol products. Dehydration was accomplished via acylation of the hydroxyl group in **13** by trifluoroacetic anhydride (TFAA) at 0 °C and subsequent elimination in the presence of triethyl amine to give **15** in 80% yield. The pivaloyloxy groups were then exchanged for the methoxy groups in 93% yield using K_2CO_3 and methyl iodide in acetone in the presence of a small amount of water. The benzyl group could not be deprotected by hydrogenation on Pd; therefore, it was removed by $AlCl_3$ in the presence of *N*,*N*-dimethylaniline as a cation scavenger in 87% yield. The target compound,

(16) Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7500–7506.

Scheme 6. Synthesis of Indanorine (**14**)



indanorine **14**, was thus prepared from 4-methylcatechol in seven steps and 39% total isolated yield.

In conclusion, we introduced a rational approach to control the course of a photochemical reaction based on an electronic-state switching strategy. A complete inversion of the reaction mechanism from α-cleavage of the C−O bond toward photoenolization was achieved by the deliberate selection of the desired electronic state by introduction of temporary "dummy" group(s) to the chromophore. They were selected from a small library of synthetically accessible candidates generated by simple and fast quantum chemical calculations. This strategy enabled us to accomplish the total synthesis of indanorine, an antiproliferative agent, involving a key photochemical step in 39% total yield. Such a strategy may also prove valuable in other fields, such as the design of new photoremovable protecting groups.

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Supporting Information Available. Experimental procedures, characterization data for products, and details on quantum chemical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.