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Nucleophile- or Light-Induced Synthesis of 3-Substituted Phthalides from 2-Formylarylketones

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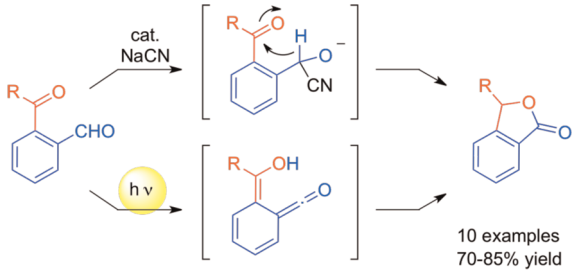
ABSTRACT



The surprisingly facile conversion (isomerization) of 2-formyl-arylketones into 3-substituted phthalides, as observed for the marine natural product pestalone and its per-*O*-methylated derivative, was investigated using a series of simple 2-acylbenzaldehydes as substrates. The transformation generally proceeds smoothly in DMSO, either in a Cannizzaro–Tishchenko-type reaction under nucleophile catalysis (NaCN) or under photochemical conditions (DMSO, 350 nm).

Phthalides, i.e. 1(3H)-isobenzofuran-1-ones, represent a relevant class of compounds because this structural motif is found in a large number of natural products,[1] synthetic pharmaceuticals,[2] and building blocks for the synthesis of more complex molecules.[3] Of particular importance are C3-substituted phthalides as exemplified by the natural products cytosporone E (**1**),[4a] fuscinarin (**2**),[4b] isopestacin (**3**),[4c] and cryphonectric acid (**4**)[4d] (Figure 1). Not surprisingly, a number of methods for the synthesis of 3-substituted phthalides have been developed, most of them exploiting either the cylization of an 1-hydroxyalkyl-substituted benzoic acid derivative[5] or the alkylation of a preformed phthalide in the 3-position.[6] Other established methods are based on the carbonylative or carboxylative *ortho*-functionalization of benzylic alcohols.[7] In recent years, several new transition-metal-catalyzed phthalide syntheses such as the Pd- or Rh-catalyzed reaction of phthalaldehyde with arylboron reagents,[8] the Ru-catalyzed cross-dehydrogenative C–H bond alkenylation of benzoic acids,[9] or the Ru- or Rh-catalyzed intramolecular hydroacylation of 2-acylylbenzaldehydes[10] have been developed.

(1) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1975; Vol. 1, pp 249–264.

(2) (a) Knepper, K.; Ziegert, R. E.; Bräse, S. T. *Tetrahedron* **2004**, *60*, 8591–8603 and references therein. (b) Hung, T. V.; Mooney, B. A.; Prager, R. H.; Tippett, J. M. *Aust. J. Chem.* **1981**, *34*, 383–395.

(3) (a) Patil, L.; Borate, H. B.; Ponde, D. E.; Deshpande, V. H. *Tetrahedron* **2002**, *58*, 6615–6620. (b) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1893–1918.

(4) (a) Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043–4046. (b) Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116–1117. (c) Strobel, G.; Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P. C. W.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179–183. (d) Arnone, A.; Assante, G.; Nasini, G.; Strada, S.; Vercesi, A. *J. Nat. Prod.* **2002**, *65*, 48–50.

(5) For recent examples, see: (a) Mangas-Sanchez, J.; Busto, E.; Gotor-Fernandez, V.; Gotor, V. *Org. Lett.* **2012**, *14*, 1444–1447. (b) Yadav, J. S.; Sreenivas, M.; Reddy, A. S.; Reddy, B. V. S. *J. Org. Chem.* **2010**, *75*, 8307–8310. (c) Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Shirai, R.; Onomura, O. *J. Org. Chem.* **2009**, *74*, 9210–9213. (d) Zhang, B.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2009**, *11*, 4712–4715.

(6) See, for instance: Singh, M.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 3121–3124.

(7) (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193–4198. (b) Larock, R. C.; Fellows, C. *J. Am. Chem. Soc.* **1982**, *104*, 1900–1907. (c) Paleo, M. R.; Lamas, C.; Castedo, L.; Dominguez, D. *J. Org. Chem.* **1992**, *57*, 2029–2033.

(8) (a) Ye, Z.; Lv, G.; Wang, W.; Zhang, M.; Cheng, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3671–3674. (b) Luo, F.; Pan, S.; Pan, C.; Qian, P.; Cheng, J. *Adv. Synth. Catal.* **2011**, *353*, 320–32.

(9) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155.

(10) (a) Phan, D.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608–15609. (b) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741–6743. See also: (c) Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6026–6027.

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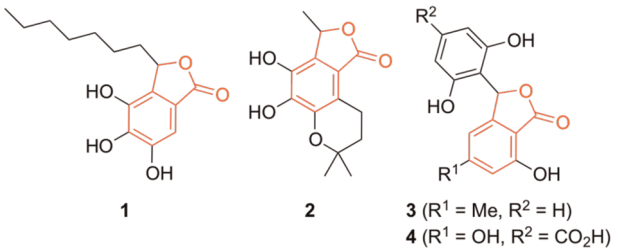
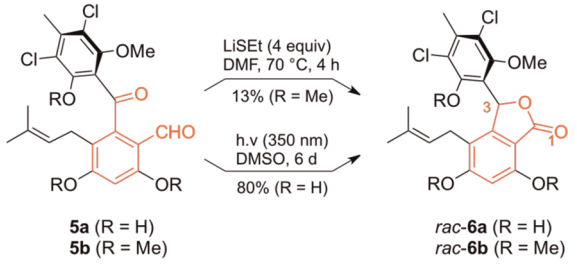


Figure 1. Selected phthalide natural products.

In the course of our recent synthesis of the marine antibiotic pestalone (**5a**)[11] we observed a surprising tendency of the permethylated analog **5b** to isomerize (disproportionate) to the 3-arylphthalide *rac*-**6b**, for instance on treatment with LiSEt as a nucleophilic reagent (usually used for the cleavage of methyl aryl ethers).[12] We also found that **5a** is cleanly converted into pestalalactone (*rac*-**6a**) by simple irradiation of a DMSO solution with UV light at 350 nm (Scheme 1).

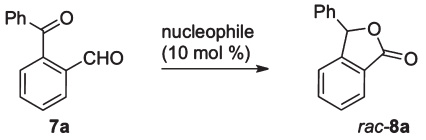
Scheme 1. Facile Isomerization of Pestalone (**5a**) and Its Permethylated Derivative **5b** to Phthalides of Type *rac*-**6** under the Action of UV Light or LiSEt (As a Nucleophile)



The surprising tendency of **5a/b** to convert to the corresponding phthalides under different conditions prompted us to probe the generality of this type of transformation using a set of 2-acylbenzaldehydes (**7**), which were readily prepared as described before[13] following the procedure of Kotali.[14]

At first, we studied the nucleophile-induced phthalide formation starting from 2-formylbenzophenone (**7a**) as a model substrate. We found that catalytic amounts (10 mol %) of a nucleophile are sufficient to achieve the desired transformation. As the results shown in Table 1 reveal, we identified NaCN as a convenient and inexpensive nucleophilic catalyst that is more effective than the originally employed LiSEt. Also, DMSO gave better results in comparison to DMF. Under the optimized conditions (10 mol % NaCN, DMSO, 4 h, 50 °C) the reaction of **7a** proceeded smoothly to afford pure *rac*-**8a** in 70% isolated yield after chromatography.

Table 1. Optimization of the Reaction Conditions[a]



entry	nucleophile	solvent	temp	yield[b]
1	LiSEt	DMF	25	32%
2	LiSEt	DMSO	25	35%
3	LiSEt	DMSO	50	39%
4	LiSEt	DMSO	100	39%
5	NaCN	DMF	50	45%
6	**NaCN**	**DMSO**	**50**	**70%**
7	NaCN	DMSO	100	60%

[a] Conditions: substrate **7a** (0.5 mmol) and nucleophile (10 mol %) in dry solvent (1.5 mL), 4 h, under argon. [b] Isolated yield.

The scope and the general efficiency of the method was then demonstrated by reacting a set of nine different *ortho*-acylbenzaldehydes under the optimized conditions. The results shown in Table 2 show that the protocol tolerates a range of functional groups, including nitro-phenyl, pyridyl, bromophenyl, anisyl, and a free phenolic OH function. The electronic properties of the substituent at the central arene unit of the substrates (**7**) had little effect on the reaction yield.

Mechanistically, we assume that the nucleophile-catalyzed transformation follows a Cannizzaro–Tishchenko-type pathway[11a,15] involving a primary attack of the nucleophilic catalyst at the aldehyde function of the substrate **7** (Scheme 2). The resulting intermediate **9** then undergoes an intramolecular hydride transfer (disproportionation) to form an alkoxide intermediate (**10**). In the final step, the lactone ring is established through a 5-*exo*-*trig* attack of the alkoxide at the carbonyl function under release of the nucleophilic catalyst.[16]

In the second part of the study, we investigated the light-induced isomerization of *ortho*-formyl-arylketones using the same set of substrates (**7a**–**i**). And indeed, on irradiation of a DMSO solution with UV light (350 nm) for 3

(11) (a) Slavov, N.; Cvengros, J.; Neudörfl, J.-M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 7588–7591. (b) For the isolation and structure elucidation of **5a**, see: (b) Cueto, M.; Jensen, P. R.; Kauffman, C.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1444–1446.

(12) Cvengros, J.; Neufeind, S.; Becker, A.; Schmalz, H. G. *Synlett* **2008**, 1993–1998.

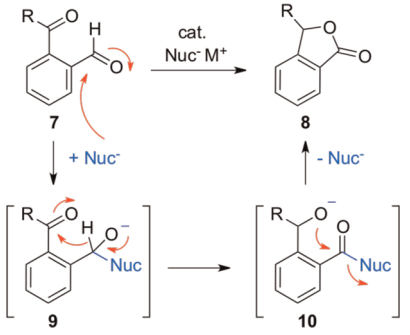
(13) Augner, D.; Gerbino, D. C.; Neudörfl, J.-M.; Schmalz, H.-G. *Org. Lett.* **2011**, *13*, 5374–5377.

(14) (a) Kotali, A.; Papapetrou, M.; Dimos, V.; Harris, P. *Org. Prep. Proc. Int.* **1998**, *30*, 177–181. (b) Kotali, A.; Tsoungas, P. G. *Tetrahedron Lett.* **1987**, *28*, 4321–4322. (c) Jacq, J.; Einhorn, C.; Einhorn, J. *Org. Lett.* **2008**, *10*, 3757–3760.

(15) (a) Cannizzaro, S. *Justus Liebigs Ann. Chem.* **1853**, *88*, 129. (b) Tishchenko, V. E. *J. Russ. Phys. Chem. Soc.* **1906**, *38*, 355–418. For a review, see: (c) Törrmäkangas, O. P.; Koskinen, A. M. P. *Recent Res. Dev. Org. Chem.* **2001**, 225–255. See also: (d) Cronin, L.; Manoni, F.; Connor, C. J. O.; Connon, S. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3045–3048.

(16) For the formation of phthalides from phthalaldehyde under solid-base catalysis, see: (a) Seki, T.; Tachikawa, H.; Yamada, T.; Hattori, H. *J. Catal.* **2003**, *217*, 117–126. For a mechanistically related reaction mediated by a *N*-heterocyclic carbene, see: (b) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558–4559.

Scheme 2. Nucleophile-Induced Conversion of 2-Formyl-arylketones (**7**) to Phthalides (**8**) through a Cannizzaro–Tishchenko-Type Mechanism



days, all compounds cleanly afforded the corresponding isobenzofuranones (*rac*-**8a**–**i**) in good isolated yields (71–85%) after chromatographic purification (Table 2). By performing the photolysis experiments in NMR tubes (employing d_6-DMSO) the reaction progress could be monitored by ^{1}H NMR (compare Figure 2) and no intermediate species could be detected this way. A control experiment in the dark ensured the necessity of light to induce the phthalide formation. In all cases, the photochemical protocol gave rise to the phthalide products (*rac*-**8a**–**i**) in slightly higher yields as compared to the NaCN-catalyzed reactions (Table 2).

A plausible mechanism for the light-induced process (Scheme 3) starts with a Norrish II type reaction and a concomitant formation of a photoenol, i.e. an enol-ketene of type **11**.[17] Assumably, this intermediate then cyclizes through intramolecular addition of the OH function to the ketene to give a 1-hydroxy-isobenzofurane (**12**) which finally tautomerizes to the more stable phthalide *rac*-**8**.

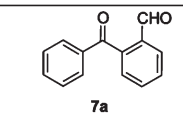
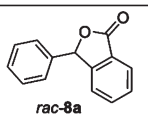
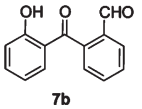
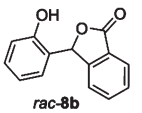
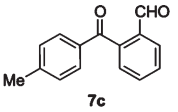
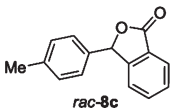
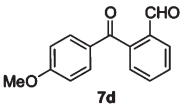
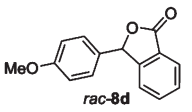
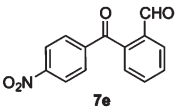
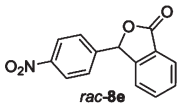
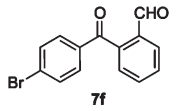
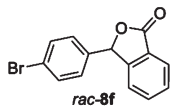
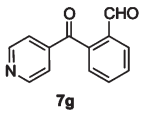
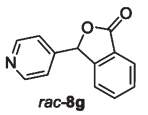
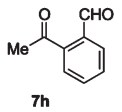
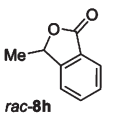
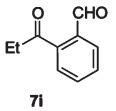
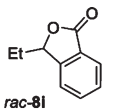
As mentioned above, the work described herein was triggered by some surprising observations made in the course of our synthesis of pestalone (**5a**).[11a] Therefore, we were in the position to probe the developed protocols once more using a sample of synthetic **5a**. To our satisfaction, treatment of **5a** with 10 mol % of NaCN in DMSO proceeded smoothly to give pure pestalalactone (*rac*-**6a**) in 62% yield after recrystallization (Scheme 4).[18]

The photochemical isomerization of **5a** into *rac*-**6a** was carefully monitored by means of ^{1}H NMR spectroscopy. Figure 1 shows the very clean conversion as indicated, for instance, by the disappearance/reappearance of the olefinic signal (H2′). An interesting observation is the doubling of certain signals (e.g., H3 and H5) in the product (*rac*-**6a**) as a consequence of a hindered rotation of the 3-aryl substituent on the NMR time scale (generation of atropdiastereomers).

(17) (a) Sato, T.; Tamura, K.; Maruyama, K.; Ogawa, O.; Imamura, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 779–783. (b) Netto-Ferreira, J. C.; Scaiano, J. C. *Can. J. Chem.* **1993**, *71*, 1209–1215. (c) Plistil, L.; Solomek, T.; Wirz, J.; Heger, D.; Klan, P. *J. Org. Chem.* **2006**, *71*, 8050–8058.

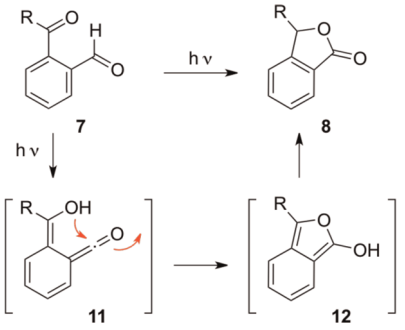
(18) The structure of *rac*-**6a** was unambiguously proven by X-ray crystallograpy (CCDC 781113).

Table 2. Conversion of Various 2-Acyl-benzaldehydes (**7**) into the Isomeric Phthalides (*rac*-**8**)[a]

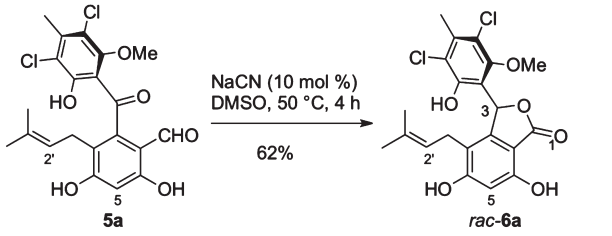
entry	substrate	product	yield[b] (NaCN)	yield[b] (hν)
1	 **7a**	 ***rac*-8a**	70%	81%
2	 **7b**	 ***rac*-8b**	73%	85%
3	 **7c**	 ***rac*-8c**	63%	79%
4	 **7d**	 ***rac*-8d**	65%	78%
5	 **7e**	 ***rac*-8e**	62%	75%
6	 **7f**	 ***rac*-8f**	61%	83%
7	 **7g**	 ***rac*-8g**	72%	74%
8	 **7h**	 ***rac*-8h**	70%	71%
9	 **7i**	 ***rac*-8i**	74%	75%

[a] Conditions: NaCN (10 mol %), DMSO, 50 °C, 4 h; or hν 35 nm, DMSO, rt, 3 d. [b] Isolated yield.

Scheme 3. Proposed Mechanism of the Light-Induced Conversion of 2-Formyl-arylketones (**7**) to Phthalides of Type **8**



Scheme 4. NaCN-Catalyzed Conversion of Pestalone (**5a**) into Pestalalactone (*rac*-**6a**)



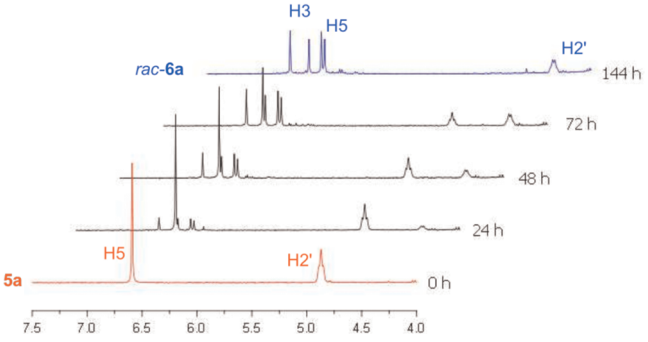


Figure 2. Monitoring the photolysis of **5a** by ^{1}H NMR (in d_6-DMSO).

In conclusion, we have developed two complementary protocols for the nucleophile- or light-induced synthesis of 3-substituted phthalides from 2-formylarylketones under mild conditions. The smooth transformations and, in particular, the ease of conversion of **5a** into *rac*-**6a** even raises the question whether the biosynthesis of natural phthalides[4] (compare Figure 1) might proceed (at least in certain cases) in a related fashion via *ortho*-formyl arylketone precursors,[19] which (in principle) could be isomerized into the corresponding phthalides under the action of a thiamine- (vitamine B_1-) derived nucleophilic carbene.[16b,20] An interesting aspect of the photochemical method developed is the proposed emergence of an enol-ketene (**11**) and an isobenzofuran (**12**) intermediate, which could possibly be trapped by an appropriate dienophile in a Diels–Alder-type reaction.[21]

The methods described here for the synthesis of phthalides can also be be classified as a redox-neutral interconversion (fusion) of two functional groups.[22] Due to the mild reaction conditions the methodology may prove of value in the context of the synthesis of more complex and highly functionalized molecules. A remaining challenge, of course, is to render the process enantioselective, for instance by employing chiral nucleophilic catalysts instead of NaCN.[23]

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Supporting Information Available. Detailed experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all phthalides prepared. This material is available free of charge via the Internet at http://pubs.acs.org. The authors declare no competing financial interest.

(19) For other natural products with an *ortho*-formylbenzophenone substructure, see: (a) Kralj, A.; Kehraus, S.; Krick, A.; Eguereva, E.; Kelter, G.; Maurer, M.; Wortmann, A.; Fiebig, H.-H.; König, G. M. *J. Nat. Prod.* **2006**, *69*, 955–1000 (Arugosin H). (b) Hashimoto, T.; Tahara, S.; Takaoka, S.; Tori, M.; Asakawa, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1528–1530 (Daldinals A–C). (c) Zhang, C.; Ondeyka, J. G.; Herath, K. B.; Guan, G.; Collado, J.; Platas, G.; Pelaez, F.; Leavitt, P. S.; Gurnett, A.; Nare, B.; Liberator, P.; Singh, S. B. *J. Nat. Prod.* **2005**, *68*, 611–613 (Tenellones A+B). (d) Hida, T.; Ishii, T.; Kanamaru, T.; Muroi, M. *J. Antibiot.* **1991**, *44*, 600–612 (TAN-931).

(20) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

(21) Compare: (a) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637–655. (b) Nicolaou, K. C.; Gray, D.; Tae, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675–3678.

(22) (a) Jurberg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 1950–1953. (b) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166–6169. (c) Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100–2103.

(23) So far, only the Rh-catalyzed intramolecular hydroacylation allows this type of reaction to proceed in an enantioselective fashion (in the presence of a chiral ligand); see ref 10a.

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