

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

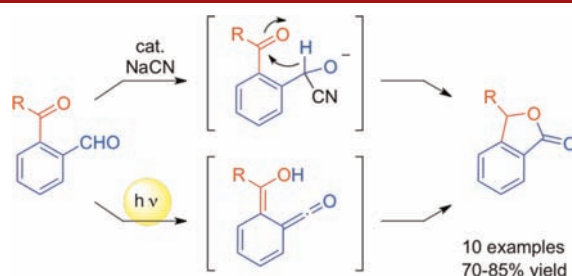
Dario C. Gerbino, Daniel Augner, Nikolay Slavov, and Hans-Günther Schmalz\*

Department of Chemistry, University of Cologne, Greinstr. 4, 50939 Köln, Germany

*schmalz@uni-koeln.de*

Received March 23, 2012

## 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,<sup>1</sup> synthetic pharmaceuticals,<sup>2</sup> and building blocks for the synthesis of more complex molecules.<sup>3</sup> Of particular importance are C3-substituted phthalides as exemplified by the natural products cytosporone E (**1**),<sup>4a</sup> fuscinarin (**2**),<sup>4b</sup> isopestacin (**3**),<sup>4c</sup> and cryphonectric acid (**4**)<sup>4d</sup> (Figure 1). Not surprisingly, a

number of methods for the synthesis of 3-substituted phthalides have been developed, most of them exploiting either the cyclization of an 1-hydroxyalkyl-substituted benzoic acid derivative<sup>5</sup> or the alkylation of a preformed phthalide in the 3-position.<sup>6</sup> Other established methods are based on the carbonylative or carboxylative *ortho*-functionalization of benzylic alcohols.<sup>7</sup> In recent years, several new transition-metal-catalyzed phthalide syntheses such as the Pd- or Rh-catalyzed reaction of phthalaldehyde with arylboron reagents,<sup>8</sup> the Ru-catalyzed cross-dehydrogenative C–H bond alkenylation of benzoic acids,<sup>9</sup> or the Ru- or Rh-catalyzed intramolecular hydroacylation of 2-acylbenzaldehydes<sup>10</sup> 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.

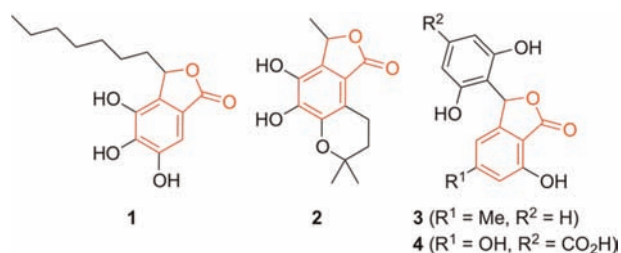
(6) See, for instance: Singh, M.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 3121–3124.

(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.

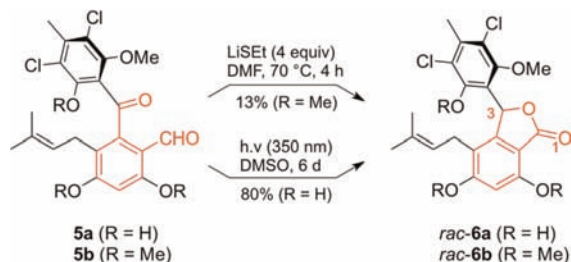
(10) (a) Phan, D.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608–15609. (b) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741–6743. See also: (c) Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6026–6027.



**Figure 1.** Selected phthalide natural products.

In the course of our recent synthesis of the marine antibiotic pestalone (**5a**)<sup>11</sup> 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).<sup>12</sup> 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<sup>13</sup> following the procedure of Kotali.<sup>14</sup>

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<sup>a</sup>

entry	nucleophile	solvent	temp	yield <sup>b</sup>
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%
<b>6</b>	<b>NaCN</b>	<b>DMSO</b>	<b>50</b>	<b>70%</b>
7	NaCN	DMSO	100	60%

<sup>a</sup> Conditions: substrate **7a** (0.5 mmol) and nucleophile (10 mol %) in dry solvent (1.5 mL), 4 h, under argon. <sup>b</sup> 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<sup>11a,15</sup> 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.<sup>16</sup>

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.

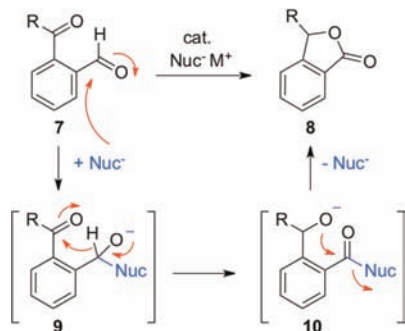
(13) Augner, D.; Gerbino, D. C.; Neudörfl, J.-M.; Schmalz, H.-G. *Org. Lett.* **2011**, *13*, 5374–5377.

(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) Törmäkangas, 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 Cannizarro–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  $^1\text{H}$  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**.<sup>17</sup> 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**).<sup>11a</sup> 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 pestalactone (*rac*-**6a**) in 62% yield after recrystallization (Scheme 4).<sup>18</sup>

The photochemical isomerization of **5a** into *rac*-**6a** was carefully monitored by means of  $^1\text{H}$  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 atrop-diastereomers).

(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.

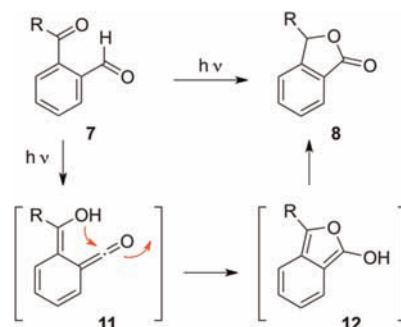
(18) The structure of *rac*-**6a** was unambiguously proven by X-ray crystallography (CCDC 781113).

**Table 2.** Conversion of Various 2-Acyl-benzaldehydes (**7**) into the Isomeric Phthalides (*rac*-**8**)<sup>a</sup>

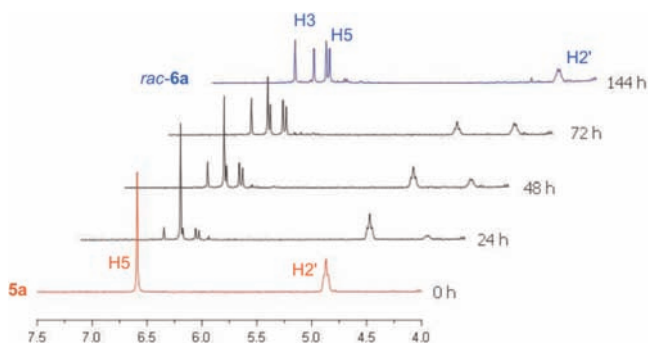
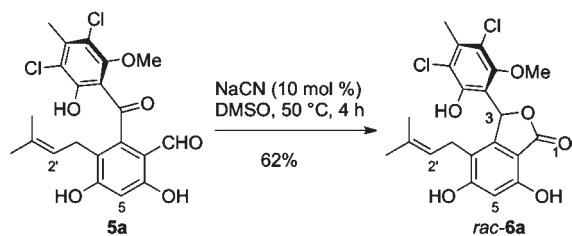
entry	substrate	product	yield <sup>b</sup> (NaCN)	yield <sup>b</sup> (h $\nu$ )
1			70%	81%
2			73%	85%
3			63%	79%
4			65%	78%
5			62%	75%
6			61%	83%
7			72%	74%
8			70%	71%
9			74%	75%

<sup>a</sup> Conditions: NaCN (10 mol %), DMSO, 50 °C, 4 h; or h $\nu$  35 nm, DMSO, rt, 3 d. <sup>b</sup> 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  $^1\text{H}$  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

(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.

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<sup>4</sup> (compare Figure 1) might proceed (at least in certain cases) in a related fashion via *ortho*-formyl arylketone precursors,<sup>19</sup> which (in principle) could be isomerized into the corresponding phthalides under the action of a thiamine- (vitamine B<sub>1</sub>-) derived nucleophilic carbene.<sup>16b,20</sup> An interesting aspect of the photochemical method developed is the proposed emergence of an enolketene (**11**) and an isobenzofuran (**12**) intermediate, which could possibly be trapped by an appropriate dienophile in a Diels–Alder-type reaction.<sup>21</sup>

The methods described here for the synthesis of phthalides can also be classified as a redox-neutral interconversion (fusion) of two functional groups.<sup>22</sup> 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.<sup>23</sup>

**Acknowledgment.** This work was supported by the Alexander von Humboldt Foundation (G. Forster post-doctoral fellowship to D.C.G.). We also thank Prof. A. Griesbeck, University of Cologne, for technical support concerning the photochemical transformations.

**Supporting Information Available.** Detailed experimental procedures, characterization data, and copies of  $^1\text{H}$  and  $^{13}\text{C}$  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.

(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.

The authors declare no competing financial interest.