RSC Advances

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides from 3-(1-Hydroxycarbethoxy/alkyl)phthalides with DEAD/PPh3/TBHP System

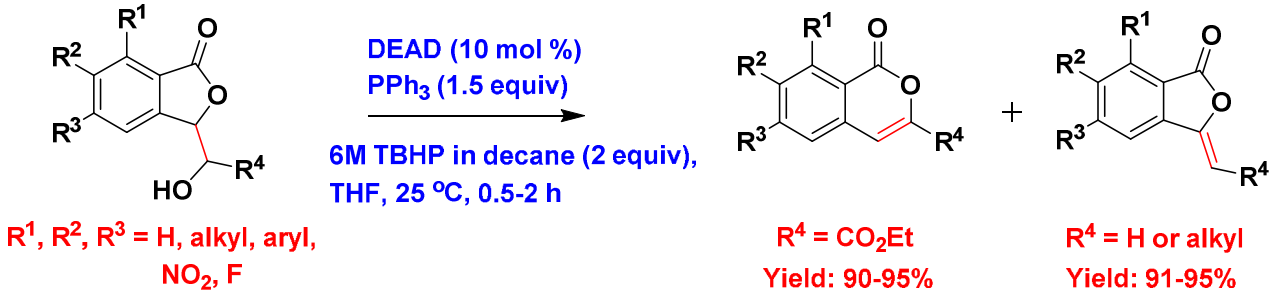
Journal:	*RSC Advances*
Manuscript ID:	RA-ART-09-2014-010372.R1
Article Type:	Paper
Date Submitted by the Author:	20-Oct-2014
Complete List of Authors:	Gadakh, Sunita; National Chemical Laboratory, CEPD Arumugam, Sudalai; National Chemical Laboratory, CE-PD

Graphical Abstract

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides from 3-(1-Hydroxycarbethoxy/alkyl)phthalides with DEAD/PPh_3/TBHP System

Sunita K. Gadakh and Arumugam Sudalai*

A single step approach for the synthesis of 3-carbethoxy-isocoumarin derivatives and 3-alkylidenephthalides from 3-(1-hydroxycarbethoxy/alkyl)phthalides is described.



R^1, R^2, R^3 = H, alkyl, aryl, NO_2, F

$R^4 = CO_2Et$
Yield: 90-95%

R^4 = H or alkyl
Yield: 91-95%

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A Simple and Efficient Synthesis of Isocoumarins and Alkylidenephthalides from 3-(1-Hydroxycarbethoxy/alkyl)phthalides with DEAD/PPh_3/TBHP System†

Sunita K. Gadakh and Arumugam Sudalai*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI:10.1039/b000000x:

A facile and novel approach to the synthesis of 3-carbethoxy-isocoumarins and 3-alkylidenephthalides is described. The methodology employs DEAD/PPh_3/TBHP as the reagent system proceeding through unprecedented 1,2-shift intramolecular ring expansion or simple elimination depending upon substituents present on 3-substituted phthalides, with broader substrate scope. This strategy is amply demonstrated in the short synthesis of bioactive molecules such as cytogenin and (*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide.

Introduction

Isocoumarins and 3-alkylidenephthalides are naturally occurring lactones, which are structural subunits present in numerous natural products (**1-3**) that exhibit a wide range of biological and pharmacological activities such as antiinflammatory, antifungal, antiplasmodic, etc.[1] They are also important in medicinal chemistry as building blocks for the synthesis of other biologically active heterocyclic[2] and carbocyclic[3] compounds. Due to their wide range of biological activities, a series of efficient methods have been developed recently for the construction of isocoumarins and 3-alkylidenephthalides frameworks (Fig. 1).

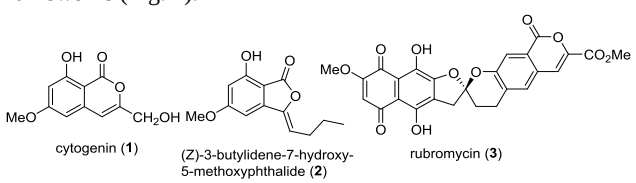
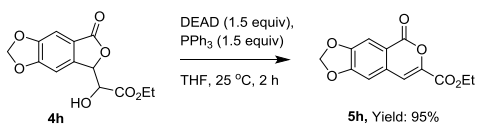


Fig. 1: Bioactive molecules with isocoumarin and alkylidenephthalide skeletons

For isocoumarins, the most useful method is based on the catalytic cyclization of o-alkynylbenzoic acid derivatives[4] while in the case of phthalides, the attractive route is the reaction between o-halobenzoic acid derivatives and terminal alkynes.[5]

Quite recently, use of copper[6] or palladium[7] salts as catalysts for the construction of isocoumarins and 3-alkylidenephthalides frameworks has attracted considerable attention due to their economic attractiveness and good functional group tolerance. Despite the efficiency of these synthetic strategies, they are significantly limited by substrate availability.[8] In addition, these methods involve multistep sequences,[9] harsh conditions,[10] expensive catalysts and ligands[11] or use of either excess acid/strong bases,[12] often leading to products with low selectivity.

Recently, we have reported a new protocol of CN-assisted cyclization for the synthesis of a wide variety of 3-substituted phthalides (**4a-t**) and their structural analogues *via* asymmetric dihydroxylation process of cyanocinnamates and styrene derivatives.[13] In continuation of this methodology, we anticipated that a simple functional group manipulation (OH→N_3)[14] in phthalide **4h** under typical Mitsunobu condition (PPh_3, DEAD, DPPA),[15] followed by reduction, would enable us to construct tetrahydroquinoline skeletons. Surprisingly, phthalide **4h**, when subjected to the above reaction condition in *stoichiometric* amounts, with or without DPPA, underwent intramolecular ring expansion to afford isocoumarin derivative **5h** exclusively in 95% yield at ambient conditions (Scheme 1).



Scheme 1: Intramolecular ring expansion of 3-(1-hydroxycarbethoxy)phthalide **4h**

* *Chemical Engineering and Process Development Division*
National Chemical Laboratoty
Pashan Road, Pune 411008, India
Fax: (+)91-02025902675
E-mail: a.sudalai@ncl.res.in

† Electronic Supplementary Information (ESI) available
Experimental details and spectral data for all the new compounds.
See DOI: 10.1039/b000000x/

Results and Discussion

Encouraged by this result, we became interested in the catalytic use of DEAD, as the stoichiometric use of DEAD leads to the formation of 1,2-dicarbethoxyhydrazine as side product, which is difficult to separate from the desired product. In the literature, it is reported that 1,2-dicarbethoxyhydrazine can be reoxidized to DEAD using iodobenzene diacetate (BIAB).[16] However, in our case, use of oxidants like BIAB, NMO, or TEMPO resulted in negligible formation of **5h**. However, other oxidants such as H_2O_2 and cumene hydroperoxide (CHP) indeed gave the desired product **5h** in 40% and 30% yields respectively (Table 1).

Table 1: Intramolecular ring expansion of phthalide **4h**: Role of oxidants and solvents[a]

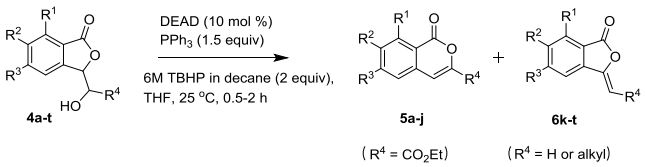
entry	oxidants (equiv)	solvents	temp (°C)	time (h)	yield of **5h** (%)[b]
1	aq. H_2O_2 (1.5)	THF	25	2	40
2	CHP (1.5)	THF	25	3.5	30
3	H_2O_2 (3)	THF	25	2	50
4	TBHP (3)	THF	25	2	70
5	TBHP (2)	1,4-dioxane	25	2	40
6	TBHP (2)	THF	50	3	40
7	TBHP (2)	THF	70	3	30
8	TBHP (2)	CH_2Cl_2	25	2.5	50
9	TBHP (3)	THF	25	2.5	50
10	TBHP (2)	Et_2O	25	1.5	30
11	TBHP (2)	CH_3CN	25	3	10
12	TBHP (2)	THF	25	2	95

[a]Reagents and conditions; phthalide **4h** (1 mmol), PPh_3 (1.5 mmol), DEAD (10 mol%). [b]Isolated yield after column chromatographic purification.

The aprotic solvents like 1,4-dioxane, CH_2Cl_2, CH_3CN and Et_2O were found to be less suitable for the reaction as compared to THF. The optimal temperature was found to be 25 °C, as at higher temperatures, there was a slight decrease in the yield (entry 6 and 7) so also in the case of the excess use of TBHP. Thus, after several experimental optimizations, the optimized conditions were determined as phthalide **4h** (1 mmol), Ph_3P (1.5 mmol) with TBHP (2 mmol) in the presence of DEAD (0.1 mmol) in THF at 25 °C to afford the desired product **5h** in 95% yield (Table 1, entry 12).

Substrates scope was then evaluated and the results are summarized in Table 2. Substrates having electron-poor or electron-rich substituents on the aromatic ring underwent the reaction smoothly to give products with excellent yields (Table 2). As can be seen from Table 2, it was observed that if the substituent $R^4 = CO_2Et$, intramolecular ring expansion took place to give isocoumarin derivatives (**5a-j**) and that if the substituents R^4 = H or alkyl, it led to simple eliminated products (**6k-t**) with *Z*-stereoselectivity. In every case, the reaction proceeded rapidly within 0.5-2 h giving the desired products (**5a-j** or **6k-t**) in excellent yields up to 95%. All the starting materials (**4a-t**) were prepared by the corresponding substituted benzaldehydes as reported in our previous work.[13]

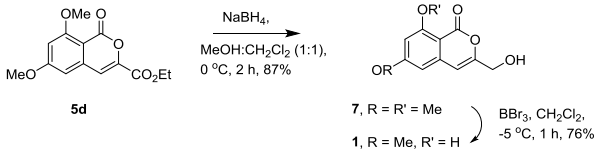
Table 2: Reaction of 3-substituted phthalides with DEAD/PPh_3/TBHP: substrate scope



entry	R^1	R^2	R^3	R^4	yield (%)[a] **5a-j**	yield (%)[a] **6k-t**
a	H	H	H	CO_2Et	94	-
b	H	OMe	H	CO_2Et	96	-
c	OMe	OMe	H	CO_2Et	92	-
d	OMe	H	OMe	CO_2Et	92	-
e	OMe	OMe	OMe	CO_2Et	90	-
f	H	OBn	OMe	CO_2Et	92	-
g	H	F	H	CO_2Et	95	-
h	H	-O-CH_2-O-		CO_2Et	95	-
i	H	NO_2	H	CO_2Et	90	-
j	(*E*)-ethyl 3-(1-cyanonaphthalene-2-yl)acrylate			CO_2Et	93	-
k	H	H	H	H	-	95
l	H	OMe	H	H	-	95
m	OMe	OMe	H	H	-	93
n	H	OMe	OMe	H	-	94
o	OMe	H	OMe	H	-	92
p	OMe	OMe	OMe	H	-	94
q	H	OBn	OMe	H	-	93
r	H	-OCH_2O-		H	-	94
s	OMe	H	OMe	Me	-	94
t	OM e	OMe	OMe	pentyl	-	91

[a]Isolated yield after column chromatographic purification.

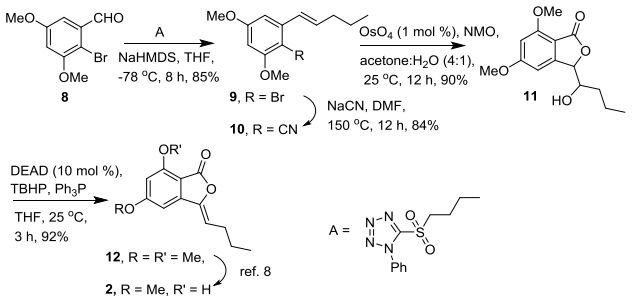
Finally, an application of this methodology is demonstrated by the short synthesis of two biologically active molecules namely cytogenin (**1**), which shows cytotoxicity and (*Z*)-3-butylidene-7-hydroxy-5-methoxyphthalide (**2**), used as antiarteriosclerotic agent. Cytogenin (**1**) was synthesized in two steps of $NaBH_4$ reduction of ester function followed by selective demethylation using BBr_3 starting from isocoumarin derivative **5d** (Scheme 2).



Scheme 2: Synthesis of cytogenin (**1**)

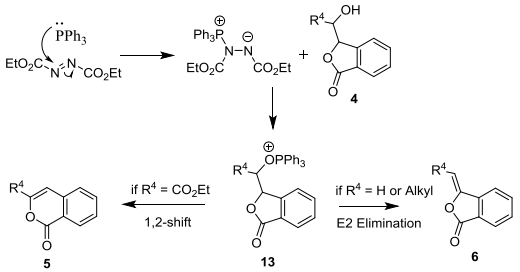
The synthesis of (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide **2** was achieved in 5 steps starting from 2-bromo-3,5-dimethoxybenzaldehyde **8**: Julia olefination of **8** gave olefin **9** (*E*:*Z* = 98:2) in 85%; bromide displacement with cyanide (84%);

Os-catalyzed dihydroxylation (90%) and TBHP-mediated Mitsunobu reaction; which led to eliminated product i.e. (*Z*)-3-butylidene-5,7-dimethoxyphthalide **12** in 80% over two steps with the required (*Z*)-selectivity. Finally, selective demethylation of **12** gave the target molecule **2** (Scheme 3).



Scheme 3: Synthesis of (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide (**2**)

A probable mechanistic pathway similar to the Mitsunobu reaction mechanism[17] is shown in Scheme **4**. Firstly, PPh_3 adds onto DEAD to generate a phosphonium ion intermediate, which readily deprotonates alcoholic proton in α-hydroxyphthalides **4** to provide phosphoxonium intermediate **13**. Intermediate **13** undergoes either ring expansion or elimination depending upon substituent R^4 and the stability of the products formed. For example, if $R^4 = CO_2Et$, it undergoes 1,2-type rearrangement of α-oxycarbocation to oxonium ion resulting in intramolecular ring expansion producing thermodynamically stable isocoumarin derivatives **5**. If R^4 = H or alkyl, it undergoes facile E2 elimination resulting in the formation of kinetic products **6**. Z-selectivity can be explained by the *anti*-E2 elimination process of β-hydrogen and Ph_3PO which is proven by NOESY NMR studies. The role of the TBHP is to reoxidize 1,2-dicarbethoxyhydrazine back to DEAD.



Scheme 4: Pathway for the formation of isocoumarin and alkylidenephthalide frameworks

Conclusion

In conclusion, we have developed a simple synthetic procedure for the preparation of 3-carbethoxy isocoumarins and 3-alkylidenephthalides directly from 3-(1-hydroxycarbethoxy/alkyl) phthalides using DEAD/PPh_3/TBHP as the reagent system. With this reagent system, intramolecular ring expansion or elimination takes place depending upon the substituents present on the phthalides (**4a-t**). This procedure is practical as the products were obtained in excellent yields showing broad substrate scope and good functional group tolerance. The methodology is amply demonstrated in the total synthesis of two bioactive molecules namely cytogenin (**1**) and (*Z*)-3-butylidene-7-hydroxy-5-methoxy phthalide (**2**).

Experimental section

General experimental procedure for the preperation of 3-substituted isocoumarins (5a-j) and alkylidenephthalides (6k-t):

To a stirred solution of 3-(1-hydroxycarbethoxy/alkyl)phthalides derivatives (**4a-t**) (1 mmol) in THF (10 mL) was added diethyl azodicarboxylate (DEAD, 10 mol%), PPh_3 (1.5 mmol) and *tert*-butyl hydroperoxide (2 mmol) and the mixture allowed to stirred at 25 °C for 0.5 to 2 h. After the completion of reaction (as monitored by TLC), THF was distilled out to give the crude product. Chromatographic purification of the crude product [silica gel (230-400 mesh) and petrolium ether: ethyl acetate (7:3) as eluent] afforded 3-substituted isocoumarin derivatives (**5a-j**) or 3-substituted alkylidene phthalides (**6k-t**) as the case may be.

Ethyl 1-oxo-1*H*-isochromene-3-carboxylate (5a)

Yield: 94%; gum; IR ($CHCl_3$, cm^{-1}): υ_{max} 684, 751, 815, 1070, 1237, 1482, 1509, 1626, 1718, 1737, 3068, 2919; ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.1 Hz, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 7.41 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 62.2, 112.0, 122.9, 127.5, 130.1, 130.6, 135.0, 135.1, 143.6, 160.2, 160.5; Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.10; H, 4.65 %.

Acknowledgements

S.K.G. thanks CSIR, New Delhi for the award of Senior Research Fellowship and DST (no. SR/S1/OC-67/2010), New Delhi, for financial support. The authors are also thankful to Dr V. V. Ranade, Chair, Chem. Engg. & Process Develop. for his constant encouragement.

References

1 (a) T. Urita, Y. Fukuyama and Y. Asakawa, *Phytochemistry*, 1986, **25**, 517; (b) K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai and S. Nakajima, *Chem. Pharm. Bull*., 1981, **29**, 2689; (c) A. C. Whyte, J. B. Gloer, J. A. Scoot and D. Mallock, *J. Nat. Prod*., 1996, **59**, 765; (d) H. Matsuda, H. Shimoda and M. Yoshikawa, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 215.

2 (a) V. Jose, G.-H. Pablo, F.-P. Roberto and M.-T. Chicotem, *Organometallics*, 2011, **30**, 1079; (b) M. A. Ciufolini and M. E. Browne, *Tetrahedron Lett*., 1986, **28**, 171; (c) I. S. Aidhen and N. S. Narasimhan, *Tetrahedron Lett*., 1989, **30**, 5323; (d) V. G. Gore, M. D. Chordia and N. S. Narasimhan, *Tetrahedron*, 1990, **46**, 2483; (e) M. D. Chordia and N. S. Narasimhan, *J. Chem. Soc. Perkin Trans. 1*, 1991, 371; (f) P. G. Ciattini, G. Mastropietro, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1993, **34**, 3763; (g) M. Lacova, S. Paulov and J. Paulovava, *J. Czech, Cs*. 1981, **190**, 783; *Chem. Abstr*., 1982, **97**, 67833v; (h) M. Lacova and M. Brondos, *Chem. Zvesti*, 1982, **36**, 245; *Chem. Abstr*. 1982, **97**, 9205z.

3 (a) R. Beugelmans, H. Ginsburg and M. J. Bois-Choussy, *Chem. Soc. Perkin Trans. 1*, 1982, 1149; (b) C. N. Lewis, J. Staunton and D. C. Sunter, *J. Chem. Soc. Perkin Trans. 1*, 1988, 747; (c) T. Minami, A. Nishimoto, Y. Nakamura and H. Hanaoka, *Chem. Pharm. Bull*., 1994, **42**, 1700.

4 (a) M. Yoshikawa, E. Harada, Y. Naitoh, K. Inoue, H. Matsuda, H. Shimoda, J. S. amahara and N. Murakami, *Chem. Pharm. Bull*., 1994, **42**, 2225; (b) S. I. Kanevskaya and S. I. Malinina, *J. Gen. Chem*. (USSR), 1956, **25**, 727; (c) J. B. Jones and A. R. Pinde, *J. Chem. Soc*., 1958, 2612.

5 (a) H.-Y. Liao and C.-H. Cheng, *J. Org. Chem.*, 1995, **60**, 3711; (b) X.-X, Guo, *J. Org. Chem*. 2013, **78**, 1660; (c) Z. Lei and H.-F. Jiang, *Tetrahedron Lett.*, 2007, **48**, 8449.

6 (a) V. Kavala, C.-C. Wang, D. K. Barange, C.-W. Kuo, P.-M. Lei and Y. Ching-Fa, *J. Org. Chem*., 2012, **77**, 5022; (b) X.-X. Guo, *J. Org. Chem*., 2013, **78**, 1660; (c) Z.-Y. Ge, X.-D. Fei, T. Tang, Y.-M. Zhu and J.-K. Shen, *J. Org. Chem*., 2012, **77**, 5736; (d) S. Cai, F. Wang and C. Xi, *J. Org. Chem*., 2012, **77**, 2331.

7 (a) H.-Y. Liao and C.-H. Cheng, *J. Org. Chem*., 1995, **60**, 3711; (b) X.-D. Fei, Z.-Y. Ge, T. Tang, Y.-M. Zhu and S.-J. Ji, *J. Org. Chem*., 2012, **77**, 10321; (c) S. A. Shahzad, C. Venin and T. Wirth, *Eur. J. Org. Chem.*, 2010, **18**, 3465; (d) D. Nandi, D. Ghosh, S.-J. Chen, B.-C. Kuo, N. M. Wang and H. M. Lee, *J. Org. Chem*., 2013, **78**, 3445.

8 R. S. Mali and K. N. Babu, *J. Org. Chem*., 1998, **63**, 2488.

9 E. Marchal, P. Uriac, B. Legouin, L. Toupet and P. van de Weghe, *Tetrahedron* 2007, **63**, 9979.

10 L. Wang and W. Shen, *Tetrahedron Lett*., 1998, **39**, 7625.

11 (a) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362; (b) S. Cai, F. Wang and C. Xi, *Synthesis*, 2012, **44**, 1892; (c) S. P. Waters and M. C. Kozlowski, *Tetrahedron Lett*., 2001, **42**, 3567; (d) F. Bellina, D. Ciucci, P. Vergamini and R. Rossi, *Tetrahedron*, 2000, **56**, 2533; (e) V. Subramanian, V. R, Batchu, D. Barange and M. Pal, *J. Org. Chem*., 2005, **70**, 4778.

12 (a) M. Brasholz, X. Luan and H.-U. Reissig, *Synthesis*, 2005, **20**, 3571; (b) M. Hellal, J.-J. Bourguignon and F. J.-J. Bihel, *Tetrahedron Lett*., 2008, **49**, 62; (c) T. P. Thrash, T. D. Welton and V. Behar, *Tetrahedron Lett.*, 2000, **41**, 29; (d) D. Qin, R. X. Ren, T. Siu, C. Zheng and S. J. Danishefsky, *Angew. Chem. Int. Ed*., 2001, **40**, 4709; (e) J. H. Park, S. V. Bhilare and S. W. Youn, *Org. Lett*., 2011, **13**, 9.

13 R. S. Reddy, I. N. Chaithanya Kiran and A. Sudalai, *Org. Biomol. Chem.*, 2012, **10**, 3655.

14 J. P. Scott, M. Alam, N. Bremeyer, A. Goodyear, T. Lam, R. D. Wilson and G. Zhou, *Org. Process Res. Dev*., 2011, **15**, 1116.

15 DEAD: diethyl azodicarboxylate, DPPA: Diphenyl phosphoryl azide.

16 T. Yuen, S. But and P. H. Toy, *J. Am. Chem. Soc*., 2006, **128**, 9636.

17 O. Mitsunobu, M. Yamada and Mukaiyama. T. *Bull. Chem. Soc. Jpn.*, 1967, **40**, 935.