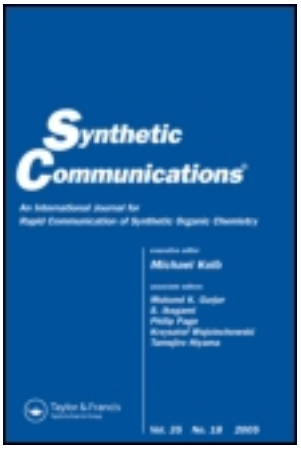


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Dual-Catalyst Acceleration of Tandem Disulfide Cleavage and Baylis-Hillman Synthesis of 2H-1-Benzothiopyran Derivatives

Dubekile Nyoni [a] , Kevin A. Lobb [a] & Perry T. Kaye [a]

[a] Department of Chemistry, Rhodes University, Grahamstown, South Africa

Accepted author version posted online: 04 Jan 2013.Version of record first published: 04 Apr 2013.

To cite this article: Dubekile Nyoni , Kevin A. Lobb & Perry T. Kaye (2013): Dual-Catalyst Acceleration of Tandem Disulfide Cleavage and Baylis-Hillman Synthesis of 2H-1-Benzothiopyran Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:13, 1837-1841

To link to this article: http://dx.doi.org/10.1080/00397911.2012.673449

Synthetic Communications®, 43: 1837–1841, 2013

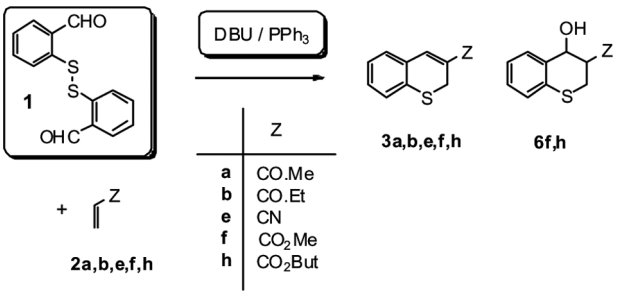
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.673449

Taylor & Francis
Taylor & Francis Group

DUAL-CATALYST ACCELERATION OF TANDEM DISULFIDE CLEAVAGE AND BAYLIS–HILLMAN SYNTHESIS OF 2*H*-1-BENZOTHIOPYRAN DERIVATIVES

Dubekile Nyoni, Kevin A. Lobb, and Perry T. Kaye
Department of Chemistry, Rhodes University, Grahamstown, South Africa

GRAPHICAL ABSTRACT



Abstract *While both 1,8-diazabicyclo[5.4.0]undec-7-ene and triphenylphosphine catalyze tandem Baylis–Hillman reaction/disulfide cleavage of 2,2′-dithiodibenzaldehyde independently, when used together as a dual-catalyst system, the overall yields of the cyclized* 2H-*1-benzothiopyrans are consistently greater and the reaction time decreases dramatically.*

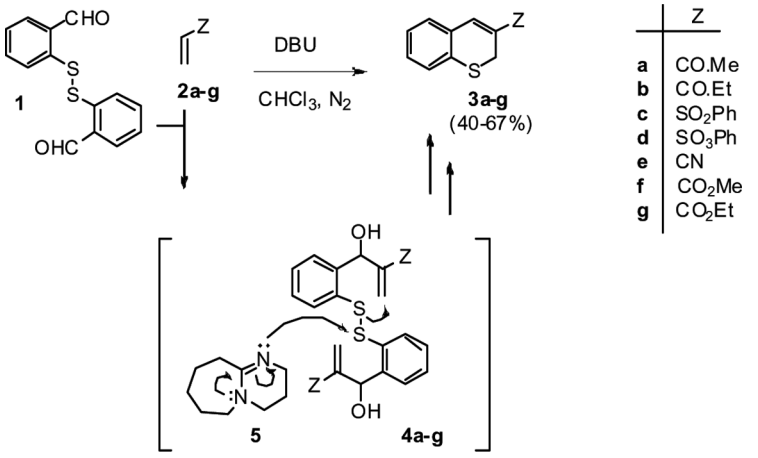
Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Baylis–Hillman reactions; 2*H*-1-benzothiopyrans; DBU-Ph_3P dual-catalyst system; disulfide cleavage

INTRODUCTION

Various approaches to the synthesis of 2*H*-1-benzothiopyrans (thiochromenes) have been reported,[1–4] and our continuing interest in the use of Baylis–Hillman methodology[5] has led to another convenient approach to these systems. Thus, reaction of 2,2′-dithiodibenzaldehyde **1** with activated alkenes **2a–g** afforded thiochromenes **3a–g** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst in one step (Scheme 1).[6] It seemed that reduction of the disufides **4a–g** was mediated by DBU, and a possible mechanistic pathway was proposed involving attack of DBU **5** on bis-Baylis–Hillman adducts **4**.[6] We have, in fact, subsequently

Received November 14, 2011.
Address correspondence to Perry T. Kaye, Department of Chemistry, Rhodes University, Grahamstown 6140, South Africa. E-mail: P.Kaye@ru.ac.za



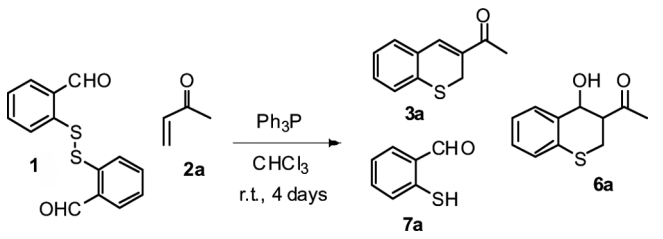
Scheme 1. DBU-mediated tandem Baylis–Hillman/disulfide cleavage/cyclization reactions to form the thiochromenes **3a–g** from 2,2′-dithiodibenzaldehyde **1**.[6]

demonstrated DBU-mediated cleavage of a range of aryl and heteroaryl disulfides,[7] and detailed kinetic and theoretical studies are being undertaken to elucidate the mechanistic pathway.

DISCUSSION

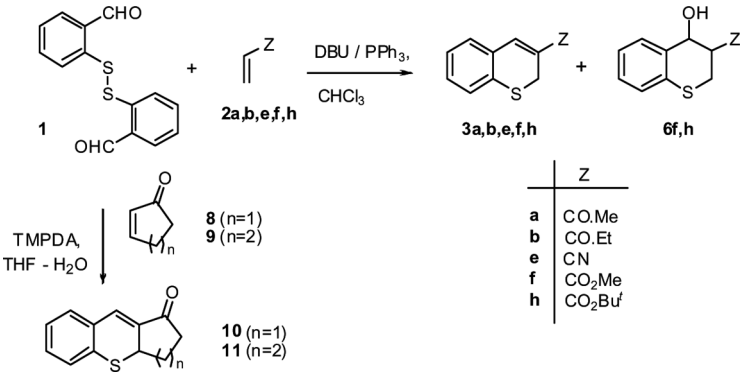
Treatment of aromatic disulfides with Ph_3P in aqueous MeOH has been shown, by Humphrey and Hawkins,[8] to afford the corresponding mercaptans, while Morita's use of tertiary phosphines[9] pre-dates Baylis and Hillman's patented use of tertiary amine catalysts.[10] In this article, we now report the results of further research directed at exploring (i) the capacity of triphenylphosphine (Ph_3P), like DBU, to effect *both* disulfide cleavage *and* catalysis of Baylis–Hillman reactions, using 2,2′-dithiodibenzaldehyde **1** as a substrate, and (ii) the combination of DBU and Ph_3P as a dual-catalyst system in the Baylis–Hillman approach to thiochromenes. The results of ongoing mechanistic and theoretical studies will be reported later.

Two exploratory experiments were run, using Ph_3P as an alternative catalyst to DBU, for the reaction of 2,2′-dithiodibenzaldehyde **1** with methyl vinyl ketone (MVK) **2a**; $CHCl_3$ was used as the solvent for one reaction and a MeOH–H_2O mixture was used for the other. Interestingly, both reactions appeared to be much slower than the reaction using DBU in $CHCl_3$. After work-up, the reaction conducted in MeOH–H_2O afforded a foul-smelling, yellow oil, which proved to be an intractable mixture. Flash chromatography of the crude material obtained from the reaction in $CHCl_3$, however, gave several products in poor yields, including 3-acetyl-2*H*-1-benzothiopyran **3a**, the mercaptan **7a**, and, following subsequent high-performance liquid chromatography (HPLC), the previously undetected diastereomeric 4-hydroxythiochromene derivative **6a** (Scheme 2). The ^1H and ^{13}C NMR spectra of the 4-hydroxy products **6a, f, h** indicate the presence of diastereomers, integration of the 4-H signal permitting estimation of the relative proportions.



Scheme 2. Ph_3P-catalyzed Baylis–Hillman reaction in $CHCl_3$.

The reaction between 2,2′-dithiodibenzaldehyde **1** and MVK **2a** was then repeated using a combination of DBU and Ph_3P as a dual-catalyst system. The reaction afforded 3-acetyl-2*H*-1-benzothiopyran **3a** in 67% yield within 2 h. Previously, the reaction using DBU as the sole catalyst had given the thiochromene **3a** in 59% yield after 24 h.[6] The dual-catalyst system (DBU/Ph_3P) was then used in reactions of 2,2′-dithiodibenzaldehyde **1** with several other activated alkenes: ethyl vinyl



Scheme 3. Baylis–Hillman reactions catalyzed by a mixture of DBU and Ph_3P or by TMPDA.

Table 1. Comparative yields of Baylis–Hillman products using DBU and DBU/PPh_3 in $CHCl_3$ (Scheme 3)

Activated alkene	Product	Yield using DBU[a] (%)	Yield using DBU/PPh_3 (%)	Time (h)[e]
MVK **2a**	**3a**	59	67	1.5–2
EVK **2b**	**3b**	67	71	1.5–2
Acrylonitrile **2e**	**3e**	52	60	2
Methyl acrylate **2f**	**3f**	40	80[b]	2–3
			34[c], 46[d]	2–3
t-Butyl acrylate **2h**	**3h**	—	80[b]	2–3
			35[c], 45[d]	2–3

[a]Yield of thiochromene **3** after ca. 2 weeks, as cited in Ref. 6.
[b]Overall yield.
[c]Yield of thiochromene **3**.
[d]Yield of the corresponding hydroxy derivative **6**.
[e]For dual-catalyst system.

ketone **2b**, acrylonitrile **2e**, methyl acrylate **2f**, and *tert*-butyl acrylate **2h** (Scheme 3). From the results summarized in Table 1, it is apparent that the overall yields (all in excess of 60%) are significantly better than those obtained using DBU alone.[6] It is also apparent that reactions involving the ketones **2a, b** and acrylonitrile **2e** gave only the corresponding thiochromene derivatives **3a, b, e**, whereas the acrylate esters **2f, h** gave the thiochromenes **3f, h** together with their 4-hydroxy derivatives **6f, h**.

N,N,N′,N′-Tetramethylpropylenediamine (TMPDA) has also been used as a catalyst for Baylis–Hillman reactions with cyclic enones[11] and, in the present study, has provided access to the known tricyclic derivatives **10** and **11** from the disulfide **1a** (Scheme 4), albeit in somewhat lower yield (39 and 20%, respectively). The thiophilicity of DBU **7** and TMPDA in these reactions may be attributable to intramolecular delocalization (Scheme 1) and ion-dipole stabilization effects,[12] respectively.

CONCLUSIONS

It is apparent from the foregoing results that DBU and TMPDA, like Ph_3P, have the capacity to *both* cleave the disulfide link in 2,2′-dithiodibenzaldehyde **1** *and* catalyze Baylis–Hillman reactions *independently*. However, when DBU and Ph_3P are used *together* as a dual-catalyst system, the yields are consistently greater and the reaction time for the tandem transformation is decreased from days or weeks to a matter of hours.

EXPERIMENTAL

NMR spectra were recorded on a Bruker 400 MHz Avance spectrometer and were referenced using solvent signals (δ_H: 7.26 ppm for residual $CHCl_3$; δ_C: 77.0 ppm for $CDCl_3$). High-resolution mass spectra (HRMS) were recorded on a Waters API-Q-TOF Ultima spectrometer (University of Stellenbosch). Melting points were determined using a hot-stage apparatus and are uncorrected. Analytical data for new and known compounds obtained in this study are provided online in the Supplementary Information.

MVK (0.11 mL) was added to a solution of 2,2′-dithiodibenzaldehyde **1** (0.125 g) and Ph_3P (0.197 g,) in $CHCl_3$ (0.6 mL), followed by DBU (0.11 mL). The resulting mixture was stirred for 1.5 h. Evaporation of the solvent in vacuo, followed by flash chromatography on silica [elution with hexane–EtOAc (2:1)] gave, as a yellow oil, 3-acetyl-2*H*-1-benzothiopyran **3a**[6] (0.12 g, 67%).

ACKNOWLEDGMENTS

The authors thank the National Research Foundation (NRF: GUN 2069255) and Rhodes University for a bursary (D.N.), and Rhodes University and the NRF for generous financial support. Any opinion, findings, conclusions, or recommendations expressed in this material are those of the authors and therefore the NRF does not accept any liability in regard thereto.

REFERENCES

1. Ingall, A. H. In *Comprehensive Heterocyclic Chemistry*; A. J. Boulton, A. McKillop (Eds.); Pergamon Press: Oxford, 1984; Vol. 3, pp. 934.
2. Tercio, J.; Ferreira, B.; Catani, V.; Comasseto, J. V. Synthesis of 2,2-dimethyl-2H-thiochromenes, the sulfur analogs of precocenes. *Synthesis* **1987**, 149.
3. Arnoldi, A.; Carughi, M. A simple synthesis of 2-substituted 1-benzothiophenes and 3-substituted 2H-1-benzothiopyrans. *Synthesis* **1988**, 155.
4. Kobayashi, K.; Konishi, H.; Kitamura, T.; Morikawa, O.; Nakahashi, R. Convenient synthesis of 1,2-dihydroquinoline-3-carboxylic acid and 2*H*-1-benzothiopyran-3-carboxylic acid derivatives. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1547.
5. (a) Bode, M. L.; Kaye, P. T. A new synthesis of indolizines via thermal cyclization of 2-pyridyl derivatives. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2612; (b) Bode, M. L.; Kaye, P. T. Indolizine studies, Part 2: Synthesis and NMR spectroscopic analysis of 2-substituted indolizines. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809; (c) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. Application of Baylis–Hillman methodology in a novel synthesis of quinoline derivatives. *Chem. Commun.* **1998**, 2563; (d) Kaye, P. T.; Nocanda, X. W. A convenient general synthesis of 3-substituted 2H-chromene derivatives. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1318.
6. Kaye, P. T.; Nocanda, X. W. A convenient Baylis–Hillman synthesis of 3-substituted 2H-1-benzothiopyrans. *Synthesis* **2001**, 2389–2392.
7. Nyoni, D.; Lobb, K. A.; Kaye, P. T.; Caira, M. R. DBU-mediated cleavage of aryl- and heteroaryl disulfides. *ARKIVOC* **2012**, (*vi*), 245–252.
8. Humphrey, R. E.; Hawkins, J. M. Reduction of aromatic disulfides with triphenylphosphine. *Anal. Chem.* **1964**, *36*, 1812.
9. Morita, K.; Suzuki, Z.; Hirose, H. Tertiary phosphine-catalyzed reaction of acrylic compounds with aldehydes. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
10. Baylis, A. B.; Hillman, M. E. D. Acrylic compounds. German Patent 2155113, 1972 *Chem. Abstr.* **1972**, *77*, 34174q.
11. Lee, K. Y.; Gowri Sanker, S.; Kim, J. N. N,N,N′,N′-Tetramethyl-1,3-propanediamine as the catalyst of choice for the Baylis–Hillman reaction of cycloalkenone: Rate acceleration by stabilizing the zwitterionic intermediate via the ion-dipole interaction. *Tetrahedron Lett.* **2004**, *45*, 5485.