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Ylide Hydrolysis in Tandem Reactions: A Highly *Z*/*E*-Selective Access to 3-Alkylidene Dihydrobenzofurans and Related Analogues

Jian-Bo Zhu, Peng Wang, Saihu Liao,* and Yong Tang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China

shliao@sioc.ac.cn; tangy@mail.sioc.ac.cn

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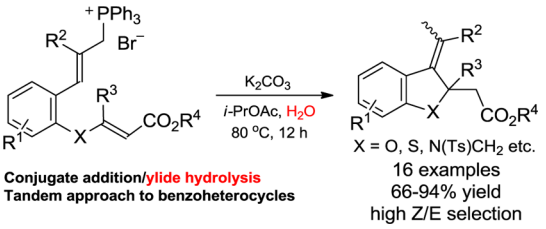
ABSTRACT



An efficient synthetic approach to benzoheterocycles has been developed based on the hydrolysis of key ylide intermediates in a tandem reaction, upon which a variety of 3-alkylidene dihydrobenzofurans and related benzoheterocyclic products can be obtained in high yields with excellent *Z*/*E* selectivity.

In the over 100-year history of phosphorus ylide chemistry, a variety of phosphorus ylide based reactions have been developed and have found widespread applications in organic synthesis, especially in the synthesis of naturally occurring products and pharmaceutics.[1] However, ylide hydrolysis, although frequently encountered in ylide reactions, is normally regarded as a side reaction that is usually avoided.[2] Its synthetic potential is far less explored and greatly underestimated. The reactions employing ylide hydrolysis have only sporadically appeared in the literature.[1,3] During our recent study on ylide-initiated Michael addition−cyclization reactions (YIMACRs),[4] we speculated that the integration of an ylide hydrolysis step in a tandem reaction to intercept the phosphonium intermediates might enable some new transformations and can be potentially useful. Hydrolysis of the betaine intermediate to cleave the C−P bond will realize, in principle, a formal reactivity umpolung of the alkyl halides (Scheme 1a), which is different from typical phosphorus ylide reactions such as the Wittig reaction and small ring formation reactions where the phosphines act more like an "RHC" unit carrier. Based on this approach, recently we successfully developed an efficient nonmetal mediated direct coupling of alkyl halides with electron-deficient alkenes for the synthesis of chromans and analogues.[5] As a continuous effort, we wish to report here the application of ylide hydrolysis to a

(1) Kolodiazhnyi, O. I. *Phosphorus Ylides: Chemistry and Application in Organic Synthesis*; Wiley-VCH: New York, 1999.

(2) For mechanistic studies, see: (a) Corfield, J. R.; Déath, N. J.; Trippett, S. *J. Chem. Soc. C* **1971**, 1930–1933. (b) Schnell, A.; Tebby, J. C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1883–1886.

(3) (a) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095–8102. (b) Schwarz, M.; Oliver, J. E.; Sonnet, P. E. *J. Org. Chem.* **1975**, *40*, 2410–2411. (c) Zaragoza, F. *J. Org. Chem.* **2002**, *67*, 4963–4964. (d) Lee, K. Y.; Na, J. E.; Lee, M. J.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5977–5981. (e) El-Dahshan, A.; Ahsanullah; Rademann, J. *Biopolymers* **2010**, *94*, 220–228. (f) Duvvuru, D.; Retailleau, P.; Betzer, J.-F.; Marinetti, A. *Eur. J. Org. Chem.* **2012**, 897–900.

(4) For reviews, see: (a) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937–948. (b) Tang, Y.; Ye, S.; Sun, X.-L. *Synlett* **2005**, *18*, 2720–2730. For selected examples, see: (c) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951–5954. (d) Wang, Q.-G.; Deng, X.-M.; Zhu, B.-H.; Ye, L.-W.; Sun, X.-L.; Li, C.-Y.; Zhu, C.-Y.; Shen, Q.; Tang, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5408–5409. (e) Han, X.; Ye, L.-W.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 3394–3397. (f) Wang, Q.-G.; Sun, X.-L.; Zheng, J.-C.; Tang, Y. *Chin. J. Chem.* **2010**, *28*, 1618–1622.

(5) Zhu, J.-B.; Wang, P.; Liao, S.; Tang, Y. *Chem. Commun.* **2013**, *49*, 4570–4572.

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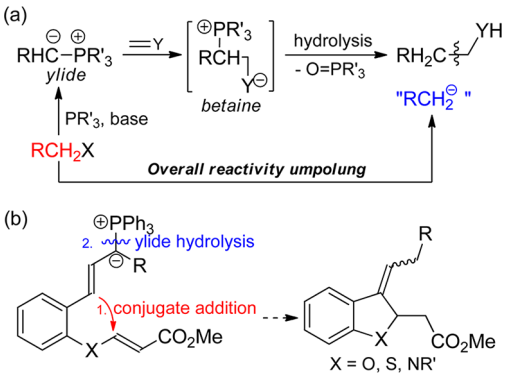
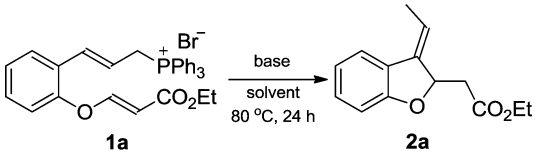
conjugate addition/hydrolysis tandem reaction of allylic ylides and the development of a new and highly *Z*/*E* selective synthetic route for 3-alkylidene 2,3-dihydrobenzofurans and related benzoheterocycles (Scheme 1b).

Scheme 1. Ylide Hydrolysis and Reaction Design



A key issue in the reaction design is the competing hydrolysis of the starting material. We envisioned that such a side reaction could be regulated by choosing suitable reaction conditions (base, solvent, etc.) to ensure the first conjugate addition is faster than the hydrolysis of the starting phosphonium salt **1a** (Table 1). We initiated our study with the screening of bases under typical reaction conditions for base-catalyzed hydrolysis of phosphorus ylides. As shown in Table 1, carbonates proved to be more suitable than stronger bases such as NaOH and *t*-BuOK (entries 1−6), and K_2CO_3 gave the optimal result. Organic base DMAP failed to deliver the desired product **2a** (entry 7). To our delight, the yield with K_2CO_3 can be further increased to 80% by using *i*-PrOAc as a solvent (entry 11). On the other hand, an elevated temperature seems critical to this reaction; reaction at room temperature furnished the desired product in 2% yield only (entry 12 vs 11). The *E*/*Z* ratios

Table 1. Reaction Optimization[a]

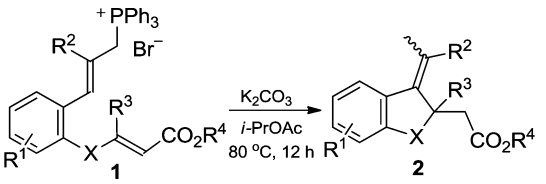


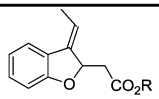
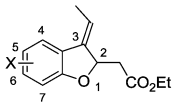
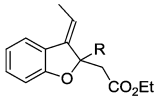
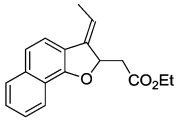
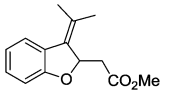
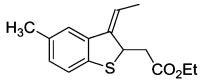
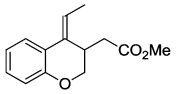
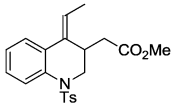
1a **2a** *E*/*Z* ~ 95:5

entry	base	solvent	yield (%)[b]
1	Na_2CO_3	DME	25
2	K_2CO_3	DME	69
3	Cs_2CO_3	DME	51
4	NaOH	DME	27
5	*t*-BuOK	DME	<5
6	NaH	DME	<5
7	DMAP	DME	<5
8	K_2CO_3	DCE	51
9	K_2CO_3	DMF	48
10	K_2CO_3	MeOAc	74
11	K_2CO_3	*i*-PrOAc	80
12[c]	K_2CO_3	*i*-PrOAc	2
13[d]	K_2CO_3	*i*-PrOAc	92

[a] Reaction conditions: **1a** (0.4 mmol), base (0.92 mmol), solvent (4 mL). [b] Isolated yield. [c] At room temperature. [d] K_2CO_3 (1.2 mmol), H_2O (1 mmol), in *i*-PrOAc (8 mL), 12 h.

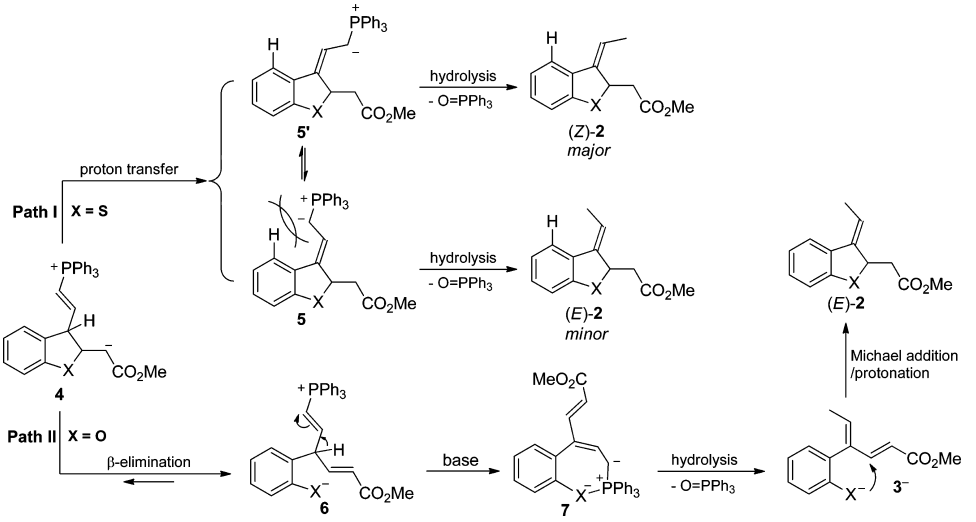
Table 2. Reaction Scope[a]



entry	product		*E*/*Z*[b]	yield (%)[c]
				
1	R = Et	**2a**	95:5	92
2	Me	**2b**	95:5	91
3	*t*-Bu	**2c**	95:5	86
				
4	X = 5-Cl	**2d**	93:7	80
5	5-Br	**2e**	92:8	83
6	5-Me	**2f**	96:4	88
7	5-OMe	**2g**	96:4	86
8	7-Me	**2h**	95:5	94
9	6-Me	**2i**	95:5	83
				
10	R = Me	**2j**	92:8	66
11	Ph	**2k**	94:6	71
12		**2l**	94:6	86
13		**2m**	_	82
14		**2n**	10:90	73
15		**2o**	93:7	84
16[d]		**2p**	>99:1	82

[a] Reaction conditions: **1** (0.4 mmol), K_2CO_3 (1.2 mmol), H_2O (1 mmol), in *i*-PrOAc (8 mL). [b] Determined by ^1H NMR of crude product. [c] Isolated yield. [d] **1p** (0.2 mmol), K_2CO_3 (0.6 mmol), H_2O (8 mmol), in *i*-PrOAc (4 mL), at 25 °C, 24 h.

Scheme 2. Proposed Pathways for the *Z* or *E* Product Formation



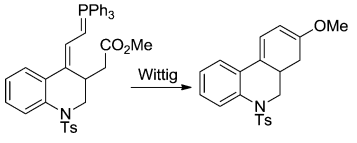
in all these entries were determined to be around 95/5 by ^{1}H NMR analysis. To our delight, adding 2.5 equiv of water significantly accelerated the reaction and further increased the yield to 92% (entry 13).[5]

Under the optimized reaction conditions, the reaction scope was investigated next and the results are tabulated in Table 2. The reactions proceeded quite well with various substrates, giving the desired 3-alkylidene 2,3-dihydrobenzofurans generally in high yields and high *E*-selectivities. The ester groups slightly influenced the yield (entries 1−3). Substrates with electron-withdrawing or -donating substituents on the aryl can all be smoothly converted to the desired 2,3-dihydrobenzofurans in high yields (entries 4−9). The current reaction also tolerates a variety of substitution patterns well on the benzene ring (entries 4−9). Notably, 2,3-dihydrobenzofurans with a C2 quaternary center are also accessible using the corresponding 3,3-disubstituted acrylates as the substrate (entries 10−11). In all cases, excellent *E*-selectivities (E/Z > 92/8) were observed (entries 1−12).

To our delight, the current transformation can be successfully extended to the synthesis of dihydrobenzothiophene **2n** (entries 14), and even to six-membered heterocycles such as chromans and tetrahydroquinolines (entries 15−16). It is worth mentioning that **2p** was obtained in high yield with perfect *E*-selectivity at room temperature, while at 80 °C ~13% of the intramolecular Wittig product[6] was isolated which was generated by the olefination reaction of the ylide intermediate with the carbonyl group of the ester (entry 16). Accordingly, a diverse range of five- and six-membered benzoheteocycles are accessible, and the current reaction provides a novel and highly Z/E selective approach to these compounds.[7]

As described above, an interesting phenomenon that was observed is the opposite Z/E selectivity between dihydrofuran and dihydrothiophene products, which also existed between the five- and six-membered cycles (entry 2 vs 15). To rationalize the reversal in the Z/E selectivity, two pathways as shown in Scheme 2 were proposed. In pathway I, the initial Michael addition product **4** first underwent a proton transfer or a double bond shift via protonation/deprotonation to generate ylide intermediate **5** and **5′**, which was then hydrolyzed to give the product **2**. The predominance of *Z*-product could be attributed to the repulsion between C4−H and the phosphonium moiety in **5′**. On the other hand, the Michael adduct **4** would undergo a retro-Michael reaction to afford **6**, followed by deprotonation, hydrolysis of ylide **7**, and an intramolecular conjugate addition, to give (*E*)-**2** as the major product (Path II). The *E*-dihydrobenzofuran products (entries 1−12) should be produced mainly through Pathway II, as a result of fast β-elimination of **4** due to the strained dihydrofuran ring[8] and the strong $O^- \cdots P^+$ interaction[1,9] in intermediate **7**. In fact, at room temperature and with the addition of 20 equiv of H_2O, the elimination product **3** (X = OH) can be isolated in 90% yield as the sole geometric isomer, and subjecting **3** to the standard reaction

(6) At 80 °C, the intramolecular Wittig product was isolated in 13% yield:

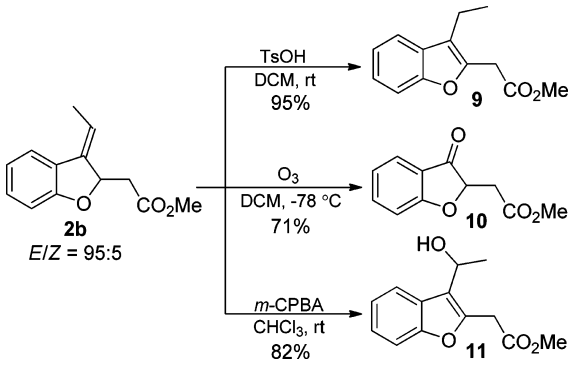


(7) (a) Le Strat, F.; Harrowven, D. C.; Maddaluno, J. *J. Org. Chem.* **2005**, *70*, 489–498. (b) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 891–893. (c) Durandetti, M.; Hardou, L.; Clément, M.; Maddaluno, J. *Chem. Commun.* **2009**, 4753–2755. (d) Okamoto, R.; Okazaki, E.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2011**, *13*, 4894–4897. (e) Durandetti, M.; Hardou, L.; Lhermet, R.; Rouen, M.; Maddaluno, J. *Chem.—Eur. J.* **2011**, *17*, 12773–12783.

(8) Katritzky, A. R.; Ramsden, C. A.; Joule, J.; Zhdankin, V. V. *Handbook of Heterocyclic Chemistry*, 3rd ed.; Elsevier: 2010, p 132.

(9) (a) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466–9468. (b) Werner, T. *Adv. Synth. Catal.* **2009**, *351*, 1469–1481. (c) Enders, D.; Nguyen, T. V. *Org. Biomol. Chem.* **2012**, 5327–5331.

Scheme 3. Selected Conversions of the Product **2b**



conditions delivered adduct **2b** in 94% yield with a >99:1 E/Z ratio; this is consistent with Path II. In addition, we prepared the phosphonium salt of intermediate **6** which can also be converted to **2b** with the same Z/E selectivity under the same conditions. In contrast, in the case of the predominant formation of Z-configured dihydrobenzothiophene **2n**, the proton-transfer pathway should be more favored over the retro-Michael route probably due to the much less strained[8] dihydrothienyl cycle (entry 14). It is noteworthy that the different inductive effect of O and S could be another factor that enhances this selectivity by changing the relative rate of proton transfer or the deprotonation (from **4** to **5**). Whereas, for the E-configured six-membered product formation (entries 15 and 16, when X = OCH_2 or N(Ts)CH_2, the priority of C3 has changed: CAr > C3), the *retro*-Michael reaction issue would not be present and products **2o** and **2p** were produced along Path I; thus the E-selection should mainly result from the steric interaction in **5** (X = OCH_2 or N(Ts)CH_2) in these cases.

The products are useful synthetic intermediates and can be readily converted to benzofuran and benzofuran-3-one derivatives.[7,10] As illustrated in Scheme 3, **2b** aromatized to 3-ethyl benzofuran **9** smoothly in the presence of a catalytic amount of TsOH. Ozonolysis can cleave the double bond to give benzofuran-3-one **10**, while treatment of **2b** with *m*-CPBA in chloroform converted **2b** into **11** in 82% yield.

In conclusion, ylide hydrolysis has been successfully integrated in a conjugate addition-initiated tandem reaction, providing a new and highly Z/E selective approach for the syntheses of a range of 3-alkylidene dihydrobenzofurans and related benzoheterocyclic compounds. Two reaction pathways were proposed to account for the substrate-dependent Z/E selectivity, and key intermediates were trapped and characterized. The strategy that discontinues a tandem reaction by intercepting ylide intermediates with hydrolysis would find more applications in developing new transformations. Application of the current method and further exploration of ylide hydrolysis in tandem reactions are ongoing in our laboratory.

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Supporting Information Available. Experimental details, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) (a) Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J.-P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D. *J. Med. Chem.* **2002**, *45*, 2788–2800. (b) Vuligonda, V.; Chandraratna, R. A. U.S. Patent 6388105, 2002. (c) Chen, C.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964–6967. (d) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. (e) Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092–8096.

The authors declare no competing financial interest.