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Facile transformation of 2-azetidinones to unsaturated ketones: application to the formal synthesis of sphingosine and phytosphingosine

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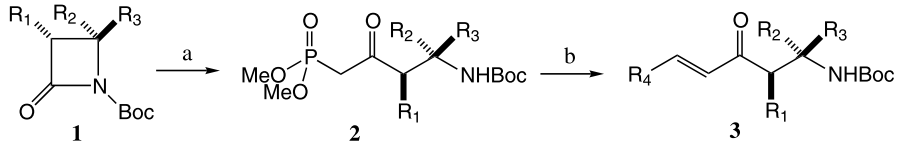
Abstract—2-Azetidinones were smoothly transformed to unsaturated ketones through the ring opening of activated 2-azetidinone by phosphonate stabilized carbanion and subsequent Horner–Wadsworth–Emmons olefination of the resulting β-ketophosphonates with aldehydes. A formal synthesis of L-*erythro*-sphingosine and D-*lyxo*-phytosphingosine from readily available 2-azetidinone was established utilizing this methodology. © 2002 Elsevier Science Ltd. All rights reserved.

Since the discovery of penicillin in 1928, 2-azetidinone (β-lactam) skeleton is well known as the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[1] As a consequence, diverse methods for practical and stereoselective ring formation of 2-azetidinone have been developed.[2] With plenty of methods for the synthesis of 2-azetidinone available, applications of 2-azetidinones as efficient chiral synthons for other classes of molecules have been subjected to many investigations.[3] For example, transformations of 2-azetidinones to nonproteogenic amino acids and peptides[3d] and ring expansion of 2-azetidinones by internal or external nucleophiles to 2-pyrrolidinones[3c] were reported.

Among the efforts in this area, recently we have reported a new synthetic methodology for 2-piperidones which could be used as versatile intermediates for the preparation of various piperidine and indolizidine alkaloids from readily accessible 2-azetidinones.[4]



a: R_1=OTBDPS, R_2=H, R_3=CH_2OTBDMS — **2a** (95%)
b: R_1=OBn, R_2=H, R_3=CH_2OTBDPS — **2b** (89%)
c: R_1=OBn, R_2=Ph, R_3=H — **2c** (88%)
d: R_1=Et, R_2=Ph, R_3=H — **2d** (59%)
e: R_1=i-Pr, R_2=Ph, R_3=H — **2e** (80%)
c, **d**, and **e** are racemic compounds

Scheme 1. *Reagents and conditions*: (a) $CH_3P(O)(OMe)_2$ (2 equiv.), *n*BuLi (2 equiv.), THF, −78°C, 30 min; (b) R_4CHO, base/solvent (see Tables 1 and 2).

Keywords: 2-azetidinone; ring-opening; Horner–Wadsworth–Emmons reaction; sphingosine; phytosphingosine.
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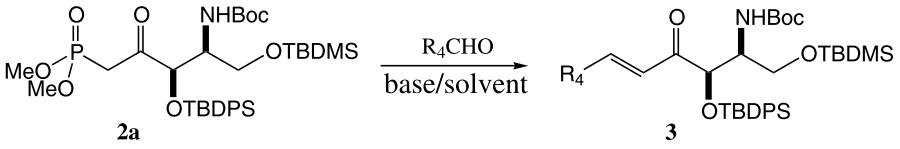
Table 1.



2a **3**

Entry	R_4CHO	Base	Solvent	Temp.	Yields (%)
1	4-Cl-PhCHO	*t*-BuOK	THF	−78°C ~ rt	69 (**3a-1**)
2	4-Cl-PhCHO	K_2CO_3	EtOH	rt	57
3	4-Cl-PhCHO	NaH	THF	0°C ~ rt	45
4	4-Cl-PhCHO	Cs_2CO_3	MeCN	rt	30
5	4-Cl-PhCHO	NaOMe	DMF	0°C ~ rt	29
6	4-Cl-PhCHO	Triton B	THF	0°C ~ rt	Trace
7	4-Cl-PhCHO	*n*-BuLi	THF	−78°C ~ rt	Trace
8	4-Cl-PhCHO	DBU/LiCl	MeCN	rt	Trace
9	CH_3CH_2CHO	K_2CO_3	EtOH	rt	89 (**3a-4**)
10	CH_3CH_2CHO	K_2CO_3	MeCN	rt	80
11	CH_3CH_2CHO	Cs_2CO_3	MeCN	rt	78
12	CH_3CH_2CHO	Cs_2CO_3	EtOH	rt	50
13	CH_3CH_2CHO	NaH	THF	0°C ~ rt	Trace
14	CH_3CH_2CHO	*t*-BuOK	THF	−78°C ~ rt	Trace

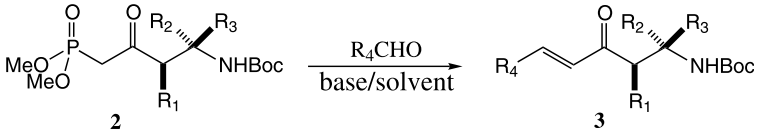
Reaction conditions: **2a** (1 equiv.), base (1.2 ~ 2.0 equiv.), 18 h.

Continuing our investigation on the utilization of 2-azetidinones as chiral synthons to other classes of molecules, we report herein the facile transformation of 2-azetidinones to unsaturated ketones through ring opening of activated 2-azetidinone by phosphonate stabilized carbanion and subsequent Horner–Wadsworth–Emmons olefination of the resulting β-ketophosphonates with aldehydes and its application to the formal synthesis of sphingosine and phytosphingosine.

It was reported that nucleophilic ring opening of *N*-Boc-2-azetidinones with simple alkyl or aryl carbanion from Grignard or organocuprate reagent produced β-amino ketone and β-amino carbinol.[5] However, when lithiated dimethyl methylphosphonate was treated to 3,4-disubstituted *N*-Boc-2-azetidinones **1**, δ-*N*-Boc-amino-β-ketophosphonates **2** were smoothly obtained as a sole product with good yields (Scheme 1).[6]

With δ-*N*-Boc-amino-β-ketophosphonates **2** in our hands, we tried to optimize HWE olefination with different aldehydes by varying base and solvent.[7] As shown in Table 1 the HWE olefination of **2a** with aliphatic and aromatic aldehydes was revealed to be highly dependent on the reaction condition of base and solvent combination. In the HWE reaction of **2a** with aromatic aldehyde of 4-chlorobenzaldehyde, *t*-BuOK–

Table 2.



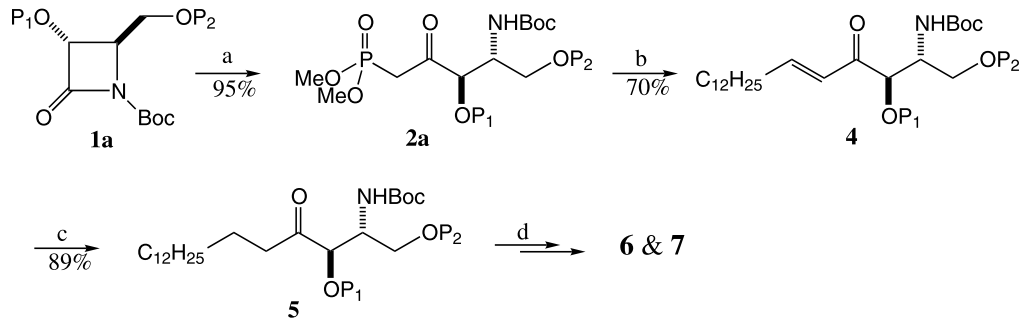
2 **3**

Entry	**2**	R_4CHO	Condition[a]	Yields of **3** (%)
1	**2a**	4-Cl-PhCHO	A	69 (**3a-1**)
2	**2a**	5-Cl-2-NO_2-PhCHO	A	52 (**3a-2**)
3	**2a**	*trans*-PhCH=CHCHO	A	66 (**3a-3**)
4	**2a**	CH_3CH_2CHO	B	89 (**3a-4**)
5	**2b**	4-Cl-PhCHO	A	53 (**3b-1**)
6	**2b**	CH_3CH_2CHO	B	53 (**3b-2**)
7	**2c**	4-Cl-PhCHO	A	63 (**3c-1**)
8	**2c**	$PhCH_2CH_2CHO$	B	45 (**3c-2**)
9	**2d**	4-Cl-PhCHO	A	56 (**3d-1**)
10	**2d**	CH_3CH_2CHO	B	68 (**3d-2**)
11	**2e**	4-Cl-PhCHO	A	56 (**3e-1**)
12	**2e**	CH_3CH_2CHO	B	64 (**3e-2**)

[a] Reaction conditions: (A: *t*-BuOK/THF, –78°C ~ rt; B: K_2CO_3/EtOH, rt, 18 h).

6: L-*erythro*-sphingosine **7**: D-*lyxo*-phytosphingosine

Figure 1.



P_1 =TBDPS, P_2 = TBDMS

Scheme 2. *Reagents and conditions*: (a) $CH_3P(O)(OMe)_2$ (2 equiv.), *n*BuLi (2 equiv.), THF, −78°C, 30 min; (b) $CH_3(CH_2)_{11}CHO$ (2 equiv.), K_2CO_3 (1.8 equiv.), EtOH, rt, 4 h; (c) H_2, Pd/C, EtOAc; (d) Ref. 9.

THF system was the choice of the reaction condition (Table 1, entry 1). On the contrary HWE reaction of **2a** with aliphatic aldehyde of propionaldehyde gave no desired product **3a**–**4** (R_4 = Et) under the same reaction conditions, but we could obtain unsaturated ketone **3a**–**4** (R_4 = Et) in the presence of K_2CO_3 in EtOH solvent in 89% yield (Table 1, entries 9 and 14).

Having optimized base–solvent systems, we examined the HWE reaction condition of **2** with different aldehydes. As shown in Table 2, HWE reaction with various aliphatic and aromatic aldehydes proceeded smoothly and afforded good yields of unsaturated ketones. In all cases, only *E* isomers of unsaturated ketones were obtained under the conditions.

With the established transformation process of 2-aetidinone to unsaturated ketone, we applied this methodology to the formal synthesis of sphingosine and phytosphingosine (Fig. 1). Sphingolipids are ubiquitous membrane components of essentially all eukaryotic cells and abundantly located in all plasma membranes as well as in some intracellular organelles.[8] Sphingosines are liphophilic components of glycosphingolipids and ceramides. Sphingosines and ceramides have been shown to play a role in intracellular signaling pathway. Phytosphingosines constitute the major base component of higher plants, protozoa, yeast and fungi, and have also been found in human kidney cerebrosides and in some cancer cell-types. Because of the importance of these compounds, even though a great number of efforts have been devoted to the synthesis of chiral sphingosines, still a lot of investigations are being pursued to produce them more efficiently.[8b,c]

HWE olefination of tridecanal with β-ketophosphonate **2a** which is derived from (3*R*,4*R*)-*N*-Boc-2-azetidinone **1a**[4,9] produced *E*-(2*R*,3*R*)-1-(TBDPS-oxy)-2-(*N*-Boc-amino)-3-(TBDMS-oxy)-4-oxo-octadeca-5-ene (**4**)[11] under the presence of K_2CO_3 in EtOH solvent in 78% yield. Hydrogenation of **4** cleanly afforded saturated ketone **5**.[11] Since transformation of *ent*-**5** to D-*erythro*-sphingosine and L-*lyxo*-phytosphingosine was already reported,[9] our synthesis of **5** constitutes formal synthesis of L-*erythro*-sphingosine and D-*lyxo*-phytosphingosine (Scheme 2).

In summary, we described facile transformation of 2-azetidinones to unsaturated ketones through the addition of phosphonate stabilized carbanion to 2-azetidinone ring and Horner–Wadsworth–Emmons olefination of the resulting β-ketophosphonates with aldehydes. We also established an efficient formal synthesis of L-*erythro*-sphingosine and D-*lyxo*-phytosphingosine from readily available 2-azetidinone from L-(+)-tartaric acid[9,10] or Bose–Manhas β-lactam[4] utilizing the present methodology.

Acknowledgements

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11. Within the limit of NMR detection, the absence of the epimerized products of the **2a** and **4** was confirmed. Spectral data of compounds **4** and **5**. **Compound 4**: $[\alpha]_D^{25}$ −5.2 (*c* 2.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.79 (s, 9H), 0.86 (t, $J=6.7$ Hz, 3H), 1.07 (s, 9H), 1.22–1.31 (m, 20H), 1.36 (s, 9H), 2.01 (dt, $J=6.8$, 6.8 Hz, 2H), 3.54 (dd, $J=10.3$, 6.3 Hz, 1H), 3.66 (dd, $J=10.3$, 5.3 Hz, 1H), 3.88–4.05 (m, 1H), 4.49 (d, $J=4.7$ Hz, 1H), 4.78 (d, $J=8.9$ Hz, 1H), 6.19 (d, $J=15.7$ Hz, 1H), 6.63 (dt, $J=15.7$, 6.8 Hz, 1H), 7.28–7.42 (m, 6H), 7.58–7.62 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.58, −5.48, 14.12, 15.47, 18.20, 19.54, 19.61, 22.68, 25.83, 26.99, 27.89, 28.31, 29.18, 29.35, 29.40, 29.50, 29.64, 31.91, 32.51, 55.15, 61.34, 76.67, 79.08, 126.39, 127.52, 127.68, 129.78, 129.87, 132.94, 133.04, 135.89, 136.00, 148.23, 155.32, 198.04. MS *m*/*z* 766 (M^+, 0.08), 652 (14), 591 (100), 492 (40), 415 (36%). **Compound 5**: $[\alpha]_D^{25}$ −3.9 (*c* 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 0.86 (t, $J=6.2$ Hz, 3H), 1.08–1.24 (m, 33H), 1.37 (s, 9H), 2.08 (dt, $J=17.5$, 7.1 Hz, 1H), 2.22 (dt, $J=17.5$, 7.2 Hz, 1H), 3.61 (dd, $J=10.0$, 6.8 Hz, 1H), 3.69 (dd, $J=10.0$, 4.7 Hz, 1H), 4.00–4.09 (m, 1H), 4.32 (d, $J=5.0$ Hz, 1H), 4.75 (d, $J=9.1$ Hz, 1H), 7.31–7.39 (m, 6H), 7.58–7.63 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.59, −5.51, 14.12, 15.45, 18.28, 19.53, 19.64, 22.69, 22.74, 25.87, 27.04, 27.88, 28.29, 28.93, 29.35, 29.60, 29.66, 31.92, 34.28, 38.85, 54.56, 61.32, 78.05, 79.32, 127.59, 127.71, 129.83, 129.90, 132.97, 133.04, 135.87, 135.98, 155.26, 209.13.; MS *m*/*z* 768 (M^+, 2), 594 (100), 494 (43), 354 (52%).