Stereoselective synthesis, reactions and antimicrobial activity of 3-vinyl-2-azetidinones

Sain Datt Sharma*, Rishi Dev Anand and Gurpreet Kaur

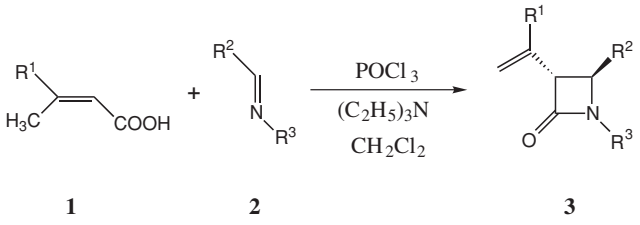
Department of Chemistry and Centre of Advanced Studies in Chemistry, Panjab University, Chandigarh-160 014, India

Stereocontrolled synthesis of 3-vinyl-2-azetidinones has been achieved by the condensation of imines and conjugated acids using phosphorus oxychloride. Transformation of these compounds to other useful intermediates has also been accomplished. Some of the compounds possess antimicrobial activity against both gram positive and gram negative bacteria.

Keywords: azetidinones, β-lactams, phosphorus oxychloride, catalytic hydrogenation, minimum inhibitory concentration

Among the variously substituted β-lactams, the 3-vinyl-2-azetidinones are efficient synthons for a variety of monocyclic[1,2] and bicyclic β-lactams[3,4] as well as pyrrolidines.[5] Whereas Zamboni and Just[6] prepared 3-vinyl as well as 3-isopropenyl-2-azetidinones as potential synthons for β-lactam antibiotics through the well known staudinger reaction, Georg *et al.*[7] used crotonic acid and Mukaiyama's reagent[8] for the synthesis of 3-vinyl-2-azetidinones. Torri *et al.*[9] developed a new method for the synthesis of 3-vinyl-2-azetidinones using palladium catalysed carbonylation of allyl diethyl phosphate in the presence of imines in an atmosphere of carbon monoxide under pressure.

Of the many important compounds of phosphorus, $POCl_3$ finds extensive use as a solvent[10] as well as a reagent. In view of its widespread applications, we have reviewed[11] the use of this easily available and comparatively inexpensive compound in organic synthesis including β-lactams.[12] We have also reported the use of this reagent for the construction of β-lactams through cyclodehydration of β-amino acids.[13] As a part of this programme, we have been successful in utilising this reagent ($POCl_3$) for the formation of 3-vinyl-2-azetidinones **3** through the direct condensation of acids with imines in the presence of triethylamine in dry dichloromethane (Scheme 1).



1 **2** **3**

Scheme 1

The reaction is highly regio- and stereoselective and the resulting 2-azetidinones are formed in good yields and with *trans* geometry of the C_3 and C_4 hydrogens. The experimental procedure is remarkably simple and does not require inert atmosphere or refluxing conditions. The versatility of the process has been proved with a wide range of Schiff bases containing electron donating and electron withdrawing groups resulting into the corresponding 2-azetidinones in excellent yields (Table 1).

Useful transformations have been reported for preparing intermediates[14-16] for carbapenem derivatives from the corresponding 3-vinylazetidin-2-ones. Here we report some reactions of the azetidin-2-one **3a** furnishing useful monocyclic β-lactams including α-alkyl β-lactams. Oxidative dearylation with cerium (IV) ammonium nitrate[17] of **3a** resulted into the *N*-unsubstituted 3-vinyl-2-azetidinone **4** in 75% yield which was *N*-alkylated using methyl iodide in the presence of sodium hydride as a base to produce *trans*-*N*-methyl-3-vinyl-2-azetidinone **5** (Scheme 2). It is known that annelation of the Schiff base of benzaldehyde and methylamine with α,β-unsaturated acid chloride produce a mixture of *cis* and *trans* β-lactams[18] in a ratio depending on the temperature of the reaction mixture. However, going through the β-lactam **4,** one can prepare the single isomer of the *N*-alkyl-β-lactam such as **5**. Hydrogenation in the presence of catalytic amount of Pd/C of the unsaturated *N*-unsubstituted 2-azetidinone **4** afforded the *trans*-α-ethyl β-lactam **6** in quantitative yield. Alternatively, β-lactam **6** was also prepared by first hydrogenating **3a** to **7** followed by oxidative dearylation (Scheme 2).

Table 1 Physical data for β-lactams **3a–i**

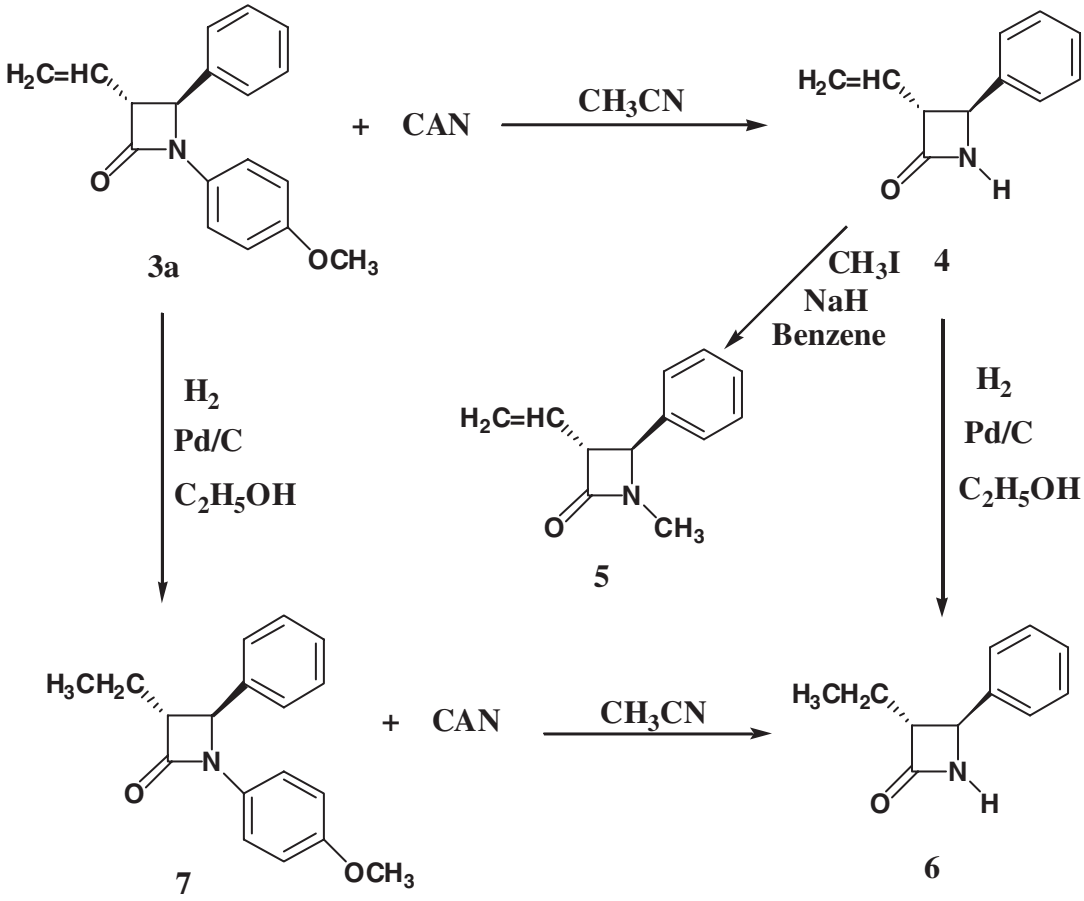
Entry	No.	R^1	R^2	R^3	Melting point/°C	Yield /%
1	**3a**	H	C_6H_5	*p*-$C_6H_4OCH_3$	115	88
2	**3b**	H	Piperonyl	*p*-$C_6H_4OCH_3$	99–100	86
3	**3c**	H	*p*-$C_6H_4OCH_3$	C_6H_5	108–110	85
4	**3d**	H	*p*-$C_6H_4OCH_3$	*p*-$C_6H_4OCH_3$	65–67	70
5	**3e**	H	C_6H_5	$(C_6H_5)_2CH$	139–140	75
6	**3f**	H	*p*-C_6H_4Cl	*p*-$C_6H_4OCH_3$	70–72	83
7	**3g**	H	*p*-C_6H_4Cl	C_6H_5	120–122	80
8	**3h**	H	2,5-$C_6H_3(OCH_3)_2$	*p*-$C_6H_4OCH_3$	98	81
9	**3i**	CH_3	C_6H_5	*p*-$C_6H_4OCH_3$	98–102	74

Some addition reactions were also performed on the terminal double bond of 2-azetidinone **3a**. Addition of bromine at 0°C afforded the dibromo product **8**. Further treatment of the dibromo compound yielded the monobromo derivative **9** which could also be prepared in a one-pot reaction[19] using the reagents shown in Scheme 3. Treatment of **3a** with *N*-bromosuccinimide–water mixture[20] yielded the bromohydrin **10**, which was identified by ^{1}H NMR data and was found identical to the one prepared by Bose[21] through epoxide ring opening.

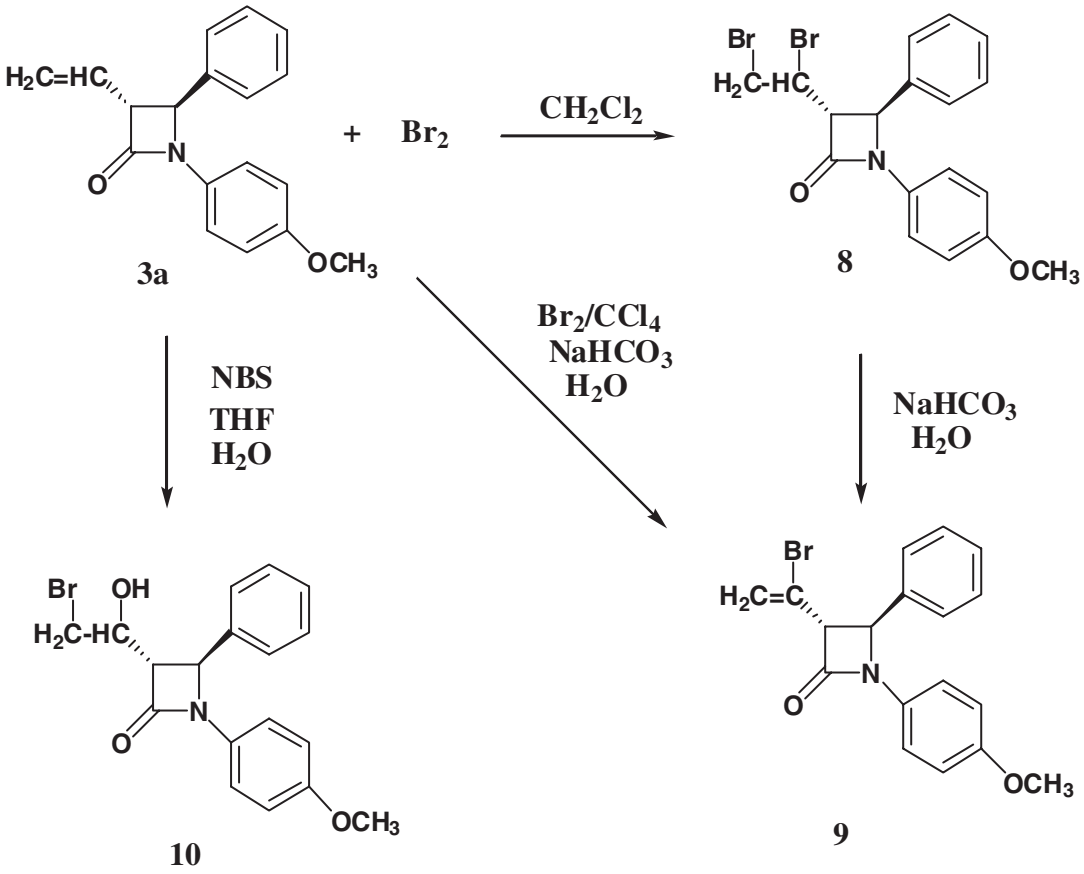
The compounds **3a** (R^1= H, R^2= Ph, R^3= *p*-$C_6H_5OCH_3$), **3g** (R^1= H, R^2= *p*-C_6H_5Cl, R^3=C_6H_5) and **3h** (R^1= H, R^2= 2,5-$C_6H_3(OCH_3)_2$) were evaluated for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Salmonella typhi* by serial dilution method. The minimum inhibitory concentration (MIC) of the compounds **3a**, **3g** and **3h** against *Salmonella typhi* was found to be 125 μg/ml. It is also worth noting that compound **3a** was found to be effective against *E.coli* and *Staphylococcus aureus* with MIC of 62.5 and 250 μg/ml respectively. Two other compounds (**3g**,**3h**), however, were found less effective against these organisms.

In conclusion, we have demonstrated the potential use of $POCl_3$ in synthesising biologically active *trans*-3-vinylazetidin-2-ones.

* Correspondent. E-mail: sdsharmapu@yahoo.com



Scheme 2



Scheme 3

Table 2 Analytical and spectroscopic data for compounds **3a–i, 4–9**

Compd	Molecular formula	Calculated (Found)/%			ν_{max}/cm^{-1} (C=O)	δ_H ($CDCl_3$)
		C	H	N		
3a	$C_{18}H_{17}NO_2$	77.40 (77.35)	6.13 (6.23)	5.01 (5.25)	1741	3.70 (m, 1H, C_3–H), 3.73 (s, 3H, $-OCH_3$), 4.7 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.35 (m, 2H, $-CH=CH_2$), 5.95(m, 1H, $-CH\equiv CH_2$), 6.7 (d, 2H, $-C_6H_4OCH_3$), 7.2 (d, 2H, $-C_6H_4OCH_3$), 7.3 (s, 5H, $-C_6H_5$).
3b	$C_{19}H_{17}NO_4$	70.58 (70.35)	5.30 (5.20)	4.33 (4.45)	1747	3.55 (m, 1H, C_3–H), 3.66 (s, 3H, $-OCH_3$), 4.5 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.22 (m, 2H, $-CH=CH_2$), 5.86 (s, 2H, methylenedioxy), 5.91 (m, 1H, $-CH=CH_2$), 6.68 (m, 5H, –ArH), 7.1 (d, 2H, *J* = 6.9 Hz, –ArH).
3c	$C_{18}H_{17}NO_2$	77.40 (77.28)	6.13 (6.23)	5.01 (5.25)	1745	3.64 (m, 1H, C_3–H), 3.78 (s, 3H, $-OCH_3$), 4.696 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.35 (m, 2H, $-CH=CH_2$), 6.06 (m, 1H, $-CH=CH_2$), 6.8–7.03 (m, 9H, –ArH).
3d	$C_{19}H_{19}NO_3$	73.77 (73.68)	6.19 (6.03)	4.53 (4.42)	1740	3.65 (m, 1H, C_3–H), 3.75 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 4.688 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.32 (m, 2H, $-CH=CH_2$), 6.0 (m, 1H, $-CH=CH_2$), 6.7 (d, 2H, $-C_6H_4OCH_3$), 6.8 (d, 2H, $-C_6H_4OCH_3$), 7.2 (m, 4H, $-C_6H_4OCH_3$).
3e	$C_{24}H_{21}NO$	84.92 (84.68)	6.24 (6.13)	4.13 (4.01)	1744	3.579 (m, 1H, C_3–H), 4.188 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.2 (m, 2H, $-CH=CH_2$), 5.5 (s, 1H, benzhydryl H), 5.8 (m, 1H, $-CH=CH_2$), 7.2 (m, 15H, $-C_6H_5$ X 3).
3f	$C_{18}H_{16}ClNO_2$	68.90 (68.78)	5.14 (5.06)	4.46 (4.35)	1742	3.63 (m, 1H, C_3–H), 3.7 (s, 3H, $-OCH_3$), 4.73 (d, 1H, *J* = 2.1 Hz, C_4–H), 5.34 (m, 2H, $-CH=CH_2$), 6.0 (m, 1H, $-CH=CH_2$), 6.75 (d, 2H, *J* = 9.0 Hz, $-C_6H_4OCH_3$), 7.1 (d, 2H, *J* = 9.0 Hz, $-C_6H_4OCH_3$), 7.26 (d, 2H, *J* = 8.7 Hz, $-C_6H_4OCl$), 7.33 (d, 2H, *J* = 8.7 Hz, $-C_6H_4OCl$).
3g	$C_{17}H_{14}ClNO$	71.96 (71.72)	4.97 (4.82)	4.94 (4.76)	1753	3.55 (m, 1H, C_3–H), 4.658 (d, 1H, *J* = 2.7 Hz, C_4–H), 5.25 (m, 2H, $-CH=CH_2$), 5.95 (m, 1H, $-CH=CH_2$), 6.9–7.3 (m 9H, –ArH).
3h	$C_{20}H_{21}NO_4$	70.78 (70.72)	6.24 (6.13)	4.13 (4.05)	1744	3.5 (m, 1H, C_3–H), 3.53 (s, 3H, $-OCH_3$), 3.6 (s, 3H, $-OCH_3$), 3.7 (s, 3H, $-OCH_3$), 4.99 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.18 (m, 1H, $-CH=CH_2$), 5.35 (m, 1H, $-CH=CH_2$), 5.95 (m, 1H, $-CH=CH_2$), 6.65 (m, 5H, –ArH), 7.125 (d, 2H, –ArH).
3i	$C_{19}H_{19}NO_2$	77.79 (77.56)	6.53 (6.23)	4.77 (4.85)	1742	1.88 (s, 3H, $-CH_3$), 3.65 (m, 1H, C_3–H), 3.7 (s, 3H, $-OCH_3$), 4.75 (d, 1H, J = 2.7 Hz, C_4–H), 4.98 (m, 2H, $-CH=CH_2$), 6.7 (d, 2H, $-C_6H_4OCH_3$), 7.2 (d, 2H, $-C_6H_4OCH_3$), 7.3 (s, 5H, $-C_6H_5$).
4	$C_{11}H_{11}NO$	76.28 (76.16)	6.40 (6.23)	8.09 (7.85)	1761	3.596 (m, 1H, C_3–H), 4.493 (d, 1H, *J* = 2.4 Hz, C_4–H), 5.284 (m, 2H, $-CH=CH_2$), 5.978 (m, 1H, $-CH=CH_2$), 7.3 (s, 5H, $-C_6H_5$).
5	$C_{12}H_{13}NO$	76.98 (76.76)	7.00 (6.83)	7.46 (7.35)	1744	2.8 (s, 3H, CH_3), 3.5 (m, 1H, C_3–H), 4.1 (d, 1H, *J* = 2.1 Hz, C_4–H), 5.15 (m, 2H, $-CH=CH_2$), 5.85 (m, 1H, $-CH=CH_2$), 7.2 (m, 5H, $-C_6H_5$).
6	$C_{11}H_{13}NO$	75.40 (75.26)	7.48 (7.23)	7.99 (8.13)	1753	1.092 (t, 3H, CH_3), 1.866 (m, 2H, $-CH_2$), 2.944 (m, 1H, C_3–H), 4.336 (d, 1H, *J* = 2.1 Hz, C_4–H), 7.298 (m, 5H, $-C_6H_5$).
7	$C_{18}H_{19}NO_2$	76.84 (76.76)	6.81 (6.73)	4.98 (4.57)	1736	1.1 (t, 3H, CH_3), 1.9 (m, 2H, $-CH_2$), 3.0 (m, 1H, C_3–H), 3.7 (s, 3H, $-OCH_3$), 4.5 (d, 1H, *J* = 2.4 Hz, C_4–H), 6.73 (d, 2H, $-C_6H_4OCH_3$), 6.75 (d, 2H, $-C_6H_4OCH_3$), 7.3 (s, 5H, $-C_6H_5$).
8	$C_{18}H_{17}Br_2NO_2$	49.23 (48.32)	3.90 (3.61)	3.19 (3.39)	1755	3.77 (s, 3H, $-OCH_3$), 3.85 (m, 2H, $-CH_2Br$), 4.07 (m, 1H, –CHBr), 4.40 (m, 1H, C_3–H), 5.338 (d, 1H, J = 2.4 Hz, C_4–H), 6.8 –7.58 (m, 9H, –ArH).
9	$C_{18}H_{16}BrNO_2$	60.35 (60.27)	4.50 (4.31)	3.91 (4.08)	1752	3.83 (s, 3H, $-OCH_3$), 4.15 (m, 1H, C_3–H), 4.43 (m, 1H, C_4–H), 4.895 (d, 1H, *J* = 2.1 Hz, olefinic H), 6.75 (d, 2H, olefinic H), 4.937 (d, 1H, *J* = 2.4 Hz, $-C_6H_4OCH_3$), 7.20 (d, 2H, $-C_6H_4OCH_3$), 7.38 (s, 5H, $-C_6H_5$).

Experimental

The IR spectra were recorded on Perkin Elmer RX I FT IR spectrophotometer and the ^{1}H NMR spectra were recorded on a 300 MHz Jeol spectrometer. The purity of the compounds was checked by TLC.

Preparation of 3-vinyl-2-azetidinones (**3**): $POCl_3$ (3 mmol) was added dropwise to a cooled solution (0°C) of Schiff base (1 mmol), α,β-unsaturated acid (1 mmol) and triethylamine (3 mmol) in methylene chloride (25 ml). The reaction mixture was stirred overnight at room temperature. The resulting solution was washed with saturated $NaHCO_3$ (25 ml), brine (25 ml), and water (25 ml × 3). Drying over anhydrous Na_2SO_4 and evaporation of the solvent yielded the desired β-lactams. Further purification was achieved by column chromatography on neutral Al_2O_3 [eluent 15% EtOAc–hexane] (see Tables 1 and 2).

Preparation of 2-azetidinones (**4, 6**): a solution of cerric (IV) ammonium nitrate (2 mmol) in water (50 ml) was added to a cooled solution (0°C) of *N*-aryl β-lactam (1 mmol) in acetonitrile (100 ml). The reaction mixture was stirred at room temperature and progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with excess water and extracted with ethyl acetate (three times). The organic layer was washed with aqueous Na_2SO_3 (25 ml), aqueous $NaHCO_3$ (25 ml), and brine (25 ml) and dried over anhydrous sodium sulfate and concentrated.

Preparation of α-alkyl-2-azetidinones (**6, 7**): Pd/C was added to a cooled solution of unsaturated β-lactam (2 mmol) in absolute ethanol (100 ml), and it was hydrogenated at 30 psi H_2 for 30 min. The reaction mixture was filtered and the filtrate concentrated to yield the desired α-alkyl β-lactam.

Preparation of N-methyl-4-phenyl-3-vinylazetidin-2-one (**5**): Sodium hydride was added to β-lactam **4** in benzene, refluxed for 30 min, then cooled and methyl iodide added. The reaction mixture was stirred at room temperature and progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was quenched with saturated solution of NH_4Cl. The organic layer was separated and washed with water and benzene was distilled to yield **5**.

Preparation of 3-(1,2-dibromoethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**8**): A solution of bromine (1 mmol) in tetrachloromethane (4 ml) is gradually introduced into a stirred solution of **3** (1 mmol) in tetrachloromethane (30 ml) at 0°C. Stirring is continued for 30 min, and the solvent is evaporated to yield **8**.

Preparation of 3-(1-bromovinyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**9**): A saturated solution of sodium hydrogen carbonate was added to solution of **8** in dichloromethane, stirred for 10–15 min, extracted with dichloromethane (25 ml), organic phase washed with water (3 × 25ml), dried with magnesium sulfate and concentrated to yield **9**.

One-pot procedure for the preparation of **9** *from* **3a**: A solution of bromine (1 mmol) in tetrachloromethane (4 ml) was gradually introduced into a stirred solution of **3a** (1 mmol) in tetrachloromethane (30 ml) at 10–15°C. Stirring is continued for 30 min, the organic phase washed thoroughly with water (3 × 25ml), saturated sodium hydrogen carbonate solution (25 ml), again water (25 ml), dried with magnesium sulfate and concentrated.

Preparation of bromohydrin 3-(2-bromo-1-hydroxyethyl)-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**10**): *N*-bromosuccinimide (1.1 mmol) was added at room temperature to 1 mmol of **3a** dissolved in 25 ml of THF–H_2O (4:1). The reaction mixture was stirred at room temperature for 2–3 h and then washed with a 10% aqueous $NaHSO_3$, dried and evaporated to furnish **10** (see Table 2).

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