# A Convenient Method for the Preparation of 3-Azetidinylidene Acetic Acid

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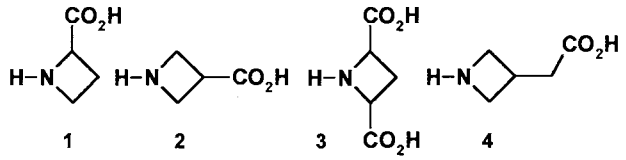
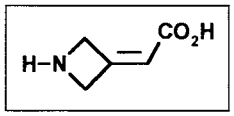
A facile route to novel 3-azetidinylidene acetic acid from commercially available epichlorohydrin is described.

Azetidine-2-carboxylic acid **1**,[1] azetidine-3-carboxylic acid **2**,[2] and azetidine-2,4-dicarboxylic acid **3**[3] have been reported to be key mimics of natural amino-acids and their biological properties have been investigated. Recently, Carruthers et al.[4] described the preparation of azetidine-3-ylacetic acid **4** as a conformationally restricted amino-acid analogue of γ-aminobutyric acid. As part of our work in the field of amino-acid mimics, we report here a straightforward synthesis of the novel 3-azetidinylidene acetic acid **5**.[5] To our knowledge, relatively few azetidine-3-ylidene derivatives have been synthesized to date. Thus, only the preparations of methyl and ethyl (1-diphenylmethyl-3-azetidinylidene) acetate, (1-diphenylmethyl-3-azetidinylidene) acetonitrile, (1-diphenylmeth- yl-3-azetidinylidene) chloromethane[6a-c] and (3-azetidinyli-dene) acetone derivatives[7] have been reported .



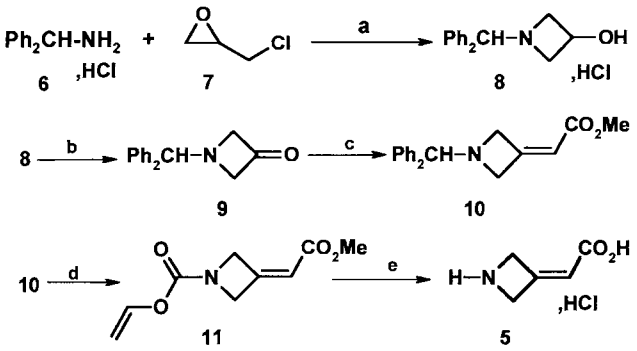
**1** **2** **3** **4**



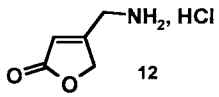
**5**

As outlined in Scheme 1, our synthetic work started from 1-diphenylmethyl-azetidin-3-one **9**[8] which was easily obtained in 50% yield by oxidation of 1-diphenylmethyl-azetidin-3-ol **8** using sulfur trioxide pyridine complex in DMSO in the presence of triethylamine. According to known procedures,[9] azetidinol hydrochloride **8** was previously synthesized in 50% yield from epichlorohydrin **7** by reaction with benzhydrylamine **6** in methanol in the presence of NaOH. Treatment of ketone **9** with methyl (triphenylphosphoranylidene)acetate under classical reaction conditions afforded the carbomethoxymethylene derivative **10**[6a] in 76% yield. The key step is the *N*-debenzhydrylation of **10** which must be performed without reduction of the double bond, this excludes the use of hydrogen, for example in the presence of Pd/C. Thus, the following procedure was applied using conditions of Olofson and coworkers[10]: i) **10** was reacted with vinyl chloroformate to afford **11** in 81% yield ; ii) reaction of **11** with 6N HCl at room temperature and subsequent lyophilization of the reaction mixture to give **5** (hydrochloride) in 73% yield.

When the reaction mixture was refluxed during 3 h, the lactone derivative **12** (hydrochloride), produced by intramolecular cyclization reaction, was isolated in 57% yield.[11]



**Scheme 1.** Synthesis of 3-azetidinylidene acetic acid **5** (Hydrochloride).
a) **6** (hydrochloride, 4.5 mol), NaOH (4.5 mol), $H_2O$ (2 L), $CH_2Cl_2$ (2 L), 12 h, rt, then organic phase dried with $MgSO_4$ and the solution evaporated to dryness followed by MeOH (1.8 L) and **7** (4.5 mol), 3 days, rt, 51%. b) *1)* **8** (0.5 mol), $CH_2Cl_2$ (300 ml), NaOH (0.58 mol) in $H_2O$ (250 ml), 1 h, rt then organic phase dried with $MgSO_4$ and the solution evaporated to dryness *2)* DMSO (1 L), TEA (4.4 mol), sulfur trioxide pyridine complex (1.7 mol), 2 h, rt then $H_2O$ (2 L), AcOEt (3x500 ml), chromatography on silica gel ($CH_2Cl_2$), 50%. c) **9** (0.23 mol), toluene, $Ph_3P{=}CHCO_2Me$ (0.23 mol), 12 h, reflux, chromatography on silica gel ($CH_2Cl_2$/MeOH 98/2), 76%. d) **10** (10 mmol), $CH_2Cl_2$, $H_2C{=}CHOCOCl$ (10 mmol), 12 h, rt, chromatography on silica gel ($CH_2Cl_2$/MeOH 99/1), 81%. e) **11** (10 mmol), 6N HCl (20 ml), 2 days, rt then lyophilization, 73%.



**12**

Synthetic procedures for **11** and **5** are as follows: To a stirred solution of **10** (2.9 g, 10 mmol) in dry dichloromethane (50 ml) vinyl chloroformate (1 g, 10 mmol) was added dropwise at room temperature under a nitrogen atmosphere. A slight exothermic reaction was observed, and the resulting mixture was stirred during 12 h. Finally, the mixture was concentrated under reduced pressure to give a yellow oil which was purified by silica gel chromatography using a dichloromethane-methanol mixture (99-1, $R_f$ 0.45) as eluent to give **11** (1.6 g , 81%) as a white solid.
A solution of **11** (1.9 g, 10 mmol) in 6N HCl (20 ml) was stirred at room temperature during 2 days until complete solubilization. The solution was directly lyophilized to afford a white solid which was washed with isopropanol (20 ml) and then methanol (2 x 10 ml) to give 1.1 g (73%) of **5** (hydrochloride) as a white solid.

## References and Notes

1 B. A. Phillips and N. H. Cromwell, *J. Heterocycles Chem.*, **10**, 795 (1973); N. H. Cromwell, *Chem. Rev.*, **79**, 331

(1979); J. E. Baldwin, M. North, and A. Flinn, *Tetrahedron Lett.*, **44**, 637 (1988); N. Verbruggen, M. Van Montagu, and E. Messens, *FEBS Lett.*, **308**, 261 (1992) and references cited therein.

2 A. G. Anderson and R. Lok, *J. Org. Chem.*, **24**, 3953 (1972) ; N. H. Cromwell and B. Phillips, *Chem. Rev.*, **79**, 331 (1979) and references cited therein.

3 A. P. Kozikowski, W. Tuckmantel, Y. Liao, H. Manev, S. Ikonomovic, and J. T. Wroblewski, *J. Med. Chem.*, **33**, 1561 (1990) ; J. Hoshino, J. Hiraoka, Y. Hata, S. Sawada, and Y. Yamamoto, *J. Chem. Soc., Perking Trans.1,* 693 (1995) and references cited therein.

4 N. I. Carruthers, S-C. Wong, and T-M. Chan, *J. Chem. Research (S),* 430 (1996).

5 Satisfactory analytical and spectroscopic data have been obtained for new azetidine derivatives. **11:** mp 52 °C, $^1$H NMR ( 250 MHz, $CDCl_3$): δ 3.70 (s, 3H, $CO_2C\underline{H}_3$), 4.5 (dd, 1H, J = 6.5 and 2 Hz, C<u>H</u>=CHO), 4.5 (bs, 2H, NC<u>H</u>$_2$), 4.8 (dd, 1H, J = 13.5 and 2 Hz, C<u>H</u>=CHO), 4.9 (bs, 2H, NC<u>H</u>$_2$), 5.9 (bs, C=C<u>H</u>-$CO_2CH_3$), 7.15 (dd, 1H, J = 13.5 and 6.5 Hz, $CH_2$=C<u>H</u>-O). $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ 51.7 (<u>C</u>$H_3$), 58.4 (N<u>C</u>$H_2$), 60.8 (N<u>C</u>$H_2$), 96.1 (<u>C</u>$H_2$=C), 114.3 (C=<u>C</u>HCO$_2$CH$_3$), 142.5 · ($CH_2$=<u>C</u>HO), 151.6 (<u>C</u>=CHCO$_2$CH$_3$), 153.6 (O<u>C</u>ON), 165.7 (<u>C</u>O$_2$CH$_3$). MS (DCI,NH3): m/z . 215 (100%) $MNH_4^+$ , IR ($CCl_4$) 1735, 1650, 1435, 1210, 1155 cm$^{-1}$. Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82 ; H,5.62 ; N, 7.10 ; O, 32.45% Found : C, 55.1 ; H, 5.6 ; N, 7.1 ; O, 32.6%. **5** (hydrochloride)**:** mp >200 °C, , $^1$H NMR (200 MHz, $CD_3CO_2D$): δ 4.7 and 4.8 (2 x s, 2 x 2H, 2 x NC<u>H</u>$_2$), 5.8 (bs, 1H, C=C<u>H</u>-$CO_2$). $^{13}$C NMR ( 50 MHz, $CD_3CO_2D$): δ 56.6 (N<u>C</u>$H_2$), 58.6 (N<u>C</u>$H_2$), 117.2 (<u>C</u>H=C), 150.8 (<u>C</u>=CHCO$_2$), 167.4 (<u>C</u>O$_2$H). MS (DCI, $NH_3$) m/z 114 $MH^+$ IR (KBr) 3300-2700, 1735, 1720, 1690 and 1180 cm$^{-1}$.

6 a) Methyl 1-diphenylmethyl-3-azetidinylidene acetate: J. L. C. Pineiro, R. A. Guiblin, V. G. Matassa, J. A. Reeve, F. Sternfeld, and J. L. Street, WO 9402477 Patent (1993); *Chem. Abstr.* **120**, 298634 (1994); Von G. Seitz and H. Hoffman, *Chemiker-Zeitung,* **10**, 440 (1976). b) Ethyl 1-diphenylmethyl-3-azetidinylidene acetate: M. E. Duggan, M. S. Ergbertson, N. Uhle, G. D. Hartman, L. M. Turchi, and W. F. Hoffman, U.S. Patent 5281585 (1992); *Chem. Abstr.* **121**, 255829 (1994). c) 1-Diphenylmethyl-3-azetidinylidene acetonitrile and 1-diphenylmethyl-3-azetidinylidene chloromethane: Von G. Seitz and H. Hoffman, *Chemiker-Zeitung,* **10**, 440 (1976).

7 P. Olesen, WO 97-11073 Patent (1995), *Chem. Abstr.* **126**; 305535 (1997).

8 Oxidation of **8** using other oxidizing agents has been reported: chromic acid in acetic acid (S. S. Chatterjee and A. Shoeb, *Synthesis,* 154 (1973) ; $(CF_3CO)_2O$ - DMSO: A. Morimoto, T. Okutani, and K. Masuda, *Chem. Pharm. Bull.*, **21**, 228 (1973); oxalyl chloride - DMSO: M. E. Duggan, M. S. Ergbertson, N. Uhle, G. D. Hartman, L. M. Turchi and W. F. Hoffman, U.S. Patent 5281585 (1992) ; *Chem. Abstr.* **121**, 255829 (1994).

9 A. G. Anderson and R. Lok, *J. Org. Chem.*, **37**, 3953 (1972), T. Okutani, T. Kaneko, and K. Masuda, *Chem. Pharm. Bull.*, **22**, 1490 (1974).

10 *N*-Dealkylation reactions with vinyl chloroformate were first described, by : R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, **18**, 1567 (1977), S. Fang, A. E. Takemori, and P. S. Portoghese, *J. Med. Chem.*, **27**, 1361 (1984).

11 $^{13}$C NMR (50 MHz , DMSO $D_6$): δ 36.3 ($CH_2N$), 72 ($CH_2O$), 117 (CH) 166 (C) 173 (CO).