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Synthesis of spirocyclic pyrrolidines: advanced building blocks for drug discovery

Bohdan A. Chalyk,[1] Maryna V. Butko,[1,2] Oksana O. Yanshyna,[1,3] Konstantin S. Gavrilenko,[1,4] Tetiana V. Druzhenko,[1,3] and Pavel K. Mykhailiuk[5]*

Abstract: Novel spirocyclic pyrrolidines were synthesized in two steps from common 3- to 7-membered (hetero)alicyclic ketones. The key transformation was the reaction between electron-deficient exocyclic alkenes with *in situ* generated *N*-benzyl azomethine ylide. The method was used to synthesize the central diamine core of the known antibacterial agents - *Sitafloxacin* and *Olamufloxacin.*

Introduction

Over the past years novel terms such as "*Scaffold hopping*,"[1] "*Escape the Flatland*"[2] and "*Conformational restriction*"[3] appeared and already changed the drug discovery. In fact, medicinal chemists have been already looking for novel 3D-shaped building blocks with high fraction of Fsp^3-hybridized carbons.[4,5]

In 2010, spirocyclic compounds were introduced as novel building blocks for drug discovery.[6] Moreover, at the moment, they have been already playing an important role in medicinal chemistry. Especially popular are the spirocyclic pyrrolidines (Figure 1).[7-9]

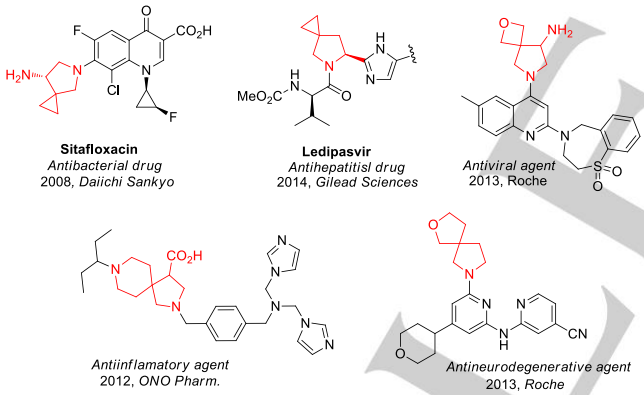

Figure 1. Drugs, bioactive compounds with spirocyclic pyrrolidines.

[*] 1) Enamine Ltd., Chervonotkatska 78, Kyiv 02094, Ukraine
Homepage: www.enamine.net
2) Department of Chemical Technology, National technical university of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute", Prosp. Peremohy 37, Kyiv 03056, Ukraine
3) Institute of High Technologies, Taras Shevchenko National University of Kyiv, Volodymyrska 60, Kyiv 01601, Ukraine
4) ChemBioCenter, Taras Shevchenko National University of Kyiv, Volodymyrska 64, Kyiv 01601, Ukraine
5) Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 64, Kyiv 01601, Ukraine
E-mail: Pavel.Mykhailiuk@gmail.com

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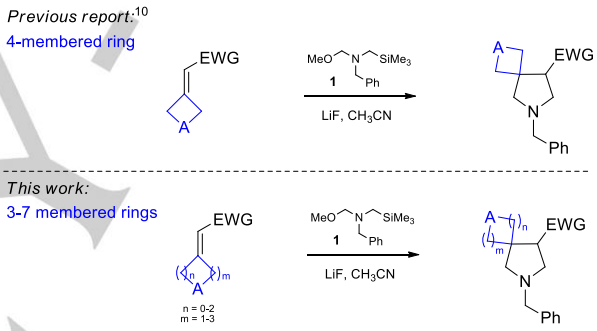
In this context, recently our group, and *Juhl* with coworkers independently developed a rapid two-step approach to spirocyclic pyrrolidines from four-membered aliphatic ketones.[10] The key reaction was the [3+2]-cycloaddition of the azomethine ylide - generated by treatment of azomethine ylide precursor **1** with LiF, - and the corresponding electron-deficient alkenes (Scheme 1).[11-13]

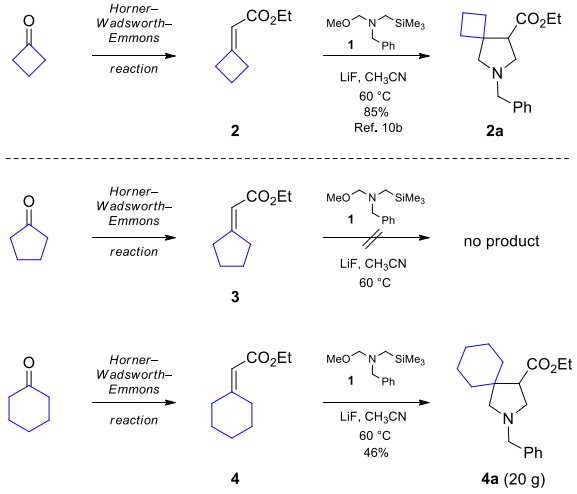
Three and six-membered (hetero)aliphatic cyclic alkenes were also used before, but very rare and not systematically. In fact, cyclopropyl-containing substrates were mentioned in only one patent,[14] while six-membered (hetero)aliphatic received a bit more attention.[10a,15,16] In this work therefore, we have systematically elaborated a practical approach to spirocyclic pyrrolidines from common 3- to 7-membered alicyclic ketones.



Scheme 1. Approaches to spirocyclic pyrrolidines.

Results and Discussion

Reaction scope. Quite recently, we showed that alkene **2** (easily obtained by *Horner-Wadsworth-Emmons* reaction of cyclobutanone) smoothly reacted with *N*-Bn azomethine ylide to

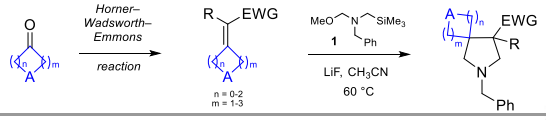


Scheme 2. Synthesis of spirocyclic pyrrolidines **2a** and **4a**.

give spirocyclic pyrrolidine **2a** in 85% yield.[10b] For the generation of the azomethine ylide, we treated reagent **1** with *cat.* LiF in acetonitrile under heating (Scheme 2).[11] Herein, we wanted to expend this strategy towards other spirocycles. Surprisingly, however, all attempts to react five-membered alkene **3** failed. Only starting material was recovered from the reaction mixture. Six-membered alkene **4**, on the contrary, gave the desired product **4a** in 46% yield. These results correlated well with the known activities of cycloalkanones: the carbonyl group of cyclopentanone is less active towards nucleophiles than that of cyclobutanone and cyclohexanone.[17]

Having a working procedure in hand, we next studied its scope. (Table 1). In fact, all three- (**5**,**6**), four- (**2**, **7**-**10**), five- (**11**-**13**), six- (**4**, **14**-**20**), and seven-membered (**21**) alkenes gave the desired spirocyclic products in good to excellent yields. The exception was cyclopentane-containing alkene **3**. Interestingly to note that heteroatoms (*N*, *O*, *S*) within the five-membered ring activated the C=C double bond by negative inductive effect, and it was enough to force the reaction to proceed. In fact, in strict contrast to alkene **3**, compounds **11**-**13** gave the desired products **11a**-**13a** in 29-53% yield.

Table 1. Reaction scope.



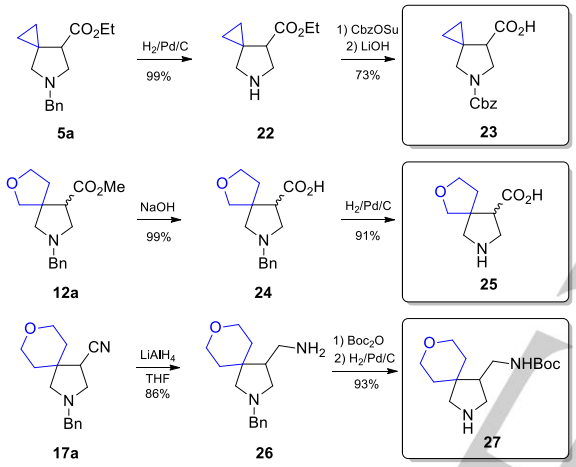
Alkene	Product	Yield[a]
5[b]	**5a**	85%
6[b]	**6a**	46%
2	**2a**	85%[c]
7	**7a**	93%[c]
8	**8a**	89%[c]
9	**9a**	83%[c]
10	**10a**	90%[c]
3	**3a**	0%
11	**11a**	29%[d]
12	**12a**	53%[d]
13	**13a**	52%[d]
4	**4a**	46%
14	**14a**	31%[10a]
15	**15a**	43%[d]
16	**16a**	33%[10a]
17	**17a**	53%
18	**18a**	53%[d]
19	**19a**	37%
20	**20a**	46%
21	**21a**	39%[d]

[a]Reagent **1**, LiF, CH_3CN, 60 °C; [b]Cyclopropanone ethyl-, TMS-ketale was used for the synthesis of alkene; [c]data were taken from Ref. 10; [d]mixture of two diastereomers.

Products **11a**-**13a**, **15a**, **18a** and **21a** were obtained as 1/1 mixture of diastereomers. Among all 3- to 7-membered substrates, the 4-membered ones were the most reactive. Other alkenes also reacted but in low yields. All syntheses were scalable: 20 g of product **4a** was obtained in one run.

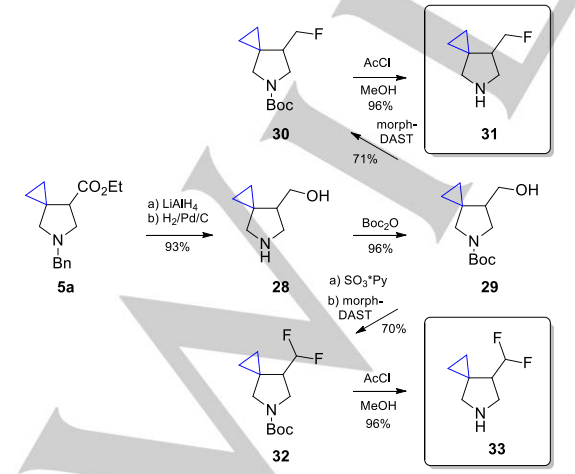
Synthesis of building blocks. Having developed a powerful tool towards the spirocyclic structures, we wanted next to synthesize several appropriately *N*-protected building blocks ready for the direct use in drug discovery projects.

In fact, removal of the *N*-Bn group in pyrrolidine **5a** by hydrogenolysis over Pd/C (**22**), followed by *N*-Cbz protection and subsequent basic hydrolysis of the ester group gave the *N*-protected amino acid **23** (Scheme 3). Analogously, amino acid **25** was synthesized from compound **12a** via the intermediate acid **24**. Reduction of nitrile **17a** with $LiAlH_4$ (**26**) followed by *N*-Boc protection, and *N*-benzyl hydrogenolysis gave the *N*-monoprotected spirocyclic diamine **27**.



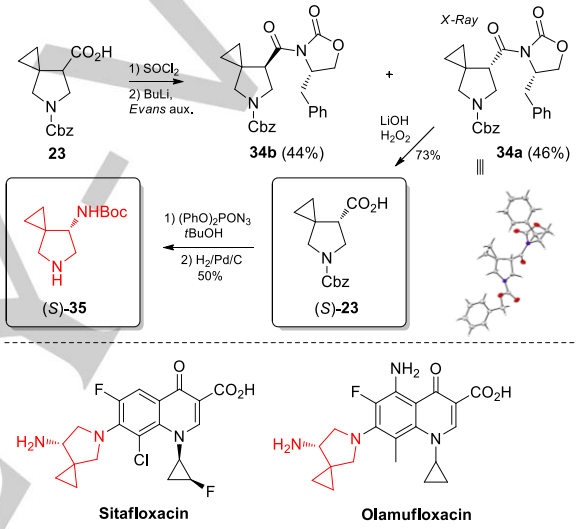
Scheme 3. Synthesis of amino acids **23** and **25**, and *N*-Boc diamine **27**.

Reduction of the ester group in **5a** with $LiAlH_4$, followed by hydrogenolysis over Pd/C gave amino alcohol **28**. *N*-Boc protection (**29**) and treatment with morpholinosulfur trifluoride (morph-DAST) gave pyrrolidine **30**. Acidic cleavage of *N*-Boc group furnished the fluoromethyl pyrrolidine **31** (Scheme 4).[18] Oxidation of alcohol **29** with Py*SO_3, followed by treatment of the intermediate aldehyde with morph-DAST gave compound **32**. Acidic cleavage of *N*-Boc group finalized the synthesis of difluoromethylated pyrrolidine **33**.



Scheme 4. Synthesis of fluorinated pyrrolidines **31** and **33**.

Synthesis of bioactive cores. We additionally developed a novel synthetic approach to optically pure diamine (*S*)-**35** – the component of antibacterial drugs *Sitafloxacin* and *Olamufloxacin* (Scheme 5).[19] Racemic acid **23** was converted with *Evans* oxazolidinone[20] into diastereomeric amides **34a** (*X-Ray*)[21] and **34b** that were separated chromatographically. Cleavage of the chiral auxiliary in **34a** gave acid (*S*)-**23**, followed by Curtius rearrangement provided the aimed diamine (*S*)-**35**.



Scheme 5. Novel synthesis of optically active diamine (*S*)-**35**.

Conclusions

We have elaborated a two-step approach to novel spirocyclic pyrrolidines from common three- to seven-membered cyclic (hetero)aliphatic ketones. The key reaction was a [3+2]-cycloaddition between electron-deficient alkenes and an *in situ* generated N-benzyl azomethine ylide. The high practical potential of the elaborated method was demonstrated by the synthesis of diamine (*S*)-**35**: the central core of the known antibacterial agents - *Sitafloxacin* and *Olamufloxacin*. Given the simplicity and availability of all starting materials, and the rapid two-step synthesis of the products, we believe that this efficient method will find practical application very soon in drug discovery within both academia and industry.

Experimental Section

Measured melting points are uncorrected. Solvents were purified according to standard procedures. Column chromatography was

performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. ^{1}H-, ^{19}F-, ^{13}C-NMR spectra were recorded on at 500 or 400 MHz, 376 MHz and 125 or 101 MHz respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI) or a GC-MS instrument with electron impact ionization (EI). LC-MS data were acquired on Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diodematrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm. Eluent, A, acetonitrile–water with 0.1% of FA (99: 1); B, water with 0.1% of FA. Optical rotations were measured on polarimeter in methanol using 1 dm cell; optical rotation values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (M) are given in mmol L^{-1}, wavelength 589 nm at 20 ºC. The enantiomeric excess and retention time (t_R) was determined for major signal by HPLCs: Daicel CHIRALPACK IA, 5 µm, 4.6 × 250 mm, Daicel CHIRALPACK IB, 5 µm, 4.6 × 250 mm, Daicel CHIRALPACK OJ-H, 5 µm, 4.6 × 250mm, Daicel CHIRALPACK AS-H, 5µm, 4.6 × 250 mm chiral columns, injection volume 0.1 µL, eluent (hexane: 2-propanol). Solid compounds were recrystalized from acetonitrile unless other is specified.

General procedure for [3+2] cycloaddition.

A 10% solution of alkene **4** (25.2 g, 0.15 mol, 1.0 equiv), reagent **1** (42.6 g, 0.18 mol, 1.2 equiv) and LiF (11.7 g, 0.45 mol, 3.0 equiv) in CH_3CN was stirred at 60 ºC for 30 h. After completion of the reaction (monitored by NMR), the reaction mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with a cold 10% solution of K_2CO_3 (2×200 mL), a saturated solution of $CuSO_4$ (3×200 mL), a cold 10% solution of K_2CO_3 (2×200 mL) and brine (1×200 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The final product was purified by distillation to afford the title compound **4a** as a colorless oil (20.7 g, 0.07 mol, 46% yield).

Ethyl 2-benzyl-2-azaspiro[4.5]decane-4-carboxylate (4a)
Yield 46%; a colorless oil.

^{1}H NMR (400 MHz, DMSO) δ 7.51 – 7.06 (m, 5H, Ph), 4.25 – 3.95 (m, 2H, C*H*$_2$CH$_3$), 3.62 (d, *J* = 13.1 Hz, 1H, C*H*HPh), 3.55 (d, *J* = 13.1 Hz, 1H, CH*H*Ph), 2.79 (t, *J* = 8.4 Hz, 1H), 2.61 (m, 3H), 2.28 (d, *J* = 9.0 Hz, 1H), 1.53 (m, 6H), 1.18 (m, 7H).

^{13}C NMR (126 MHz, DMSO) δ 172.8 (s, *C*O$_2$Et), 139.7 (s, Ph, *C*), 128.7 (s, Ph, *C*H), 128.6 (s, Ph, *C*H), 127.2 (s, Ph, *C*H), 63.3 (s), 60.2 (s), 59.9 (s), 55.4 (s), 54.2 (s), 45.7 (s), 38.1 (s), 33.1 (s), 26.0 (s), 24.1 (s), 23.3 (s), 14.7 (s, *C*H$_3$).

MS (EI, *m/z*): 301 (M$^+$).

Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.97; H, 9.34; N, 4.96.

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Keywords: building blocks • drug discovery • pyrrolidine • azomethine ylide • spirocycles

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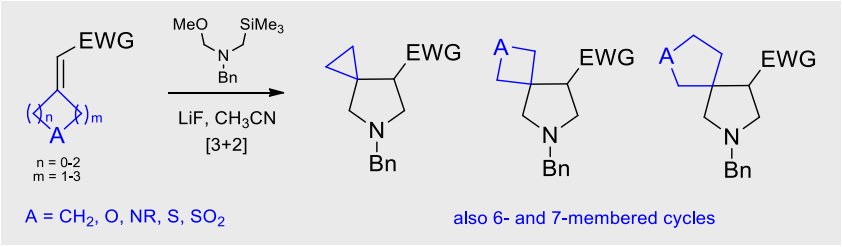

Spirocyclic pyrrolidines

*B. A. Chalyk, M. V. Butko, O. O. Yanshyna, K. S. Gavrilenko, T. V. Druzhenko, P. K. Mykhailiuk**

Synthesis of spirocyclic pyrrolidines: advanced building blocks for drug discovery.

Novel spirocyclic pyrrolidines were synthesized in two steps from common 3- to 7-membered (hetero)alicyclic ketones. The key transformation was the reaction between electron-deficient exocyclic alkenes with *in situ* generated *N*-benzyl azomethine ylide. The method was used to synthesize the central diamine core of the known antibacterial agents - *Sitafloxacin* and *Olamufloxacin.*