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A Novel Strategy for the Synthesis of 3-(*N*-Heteryl)pyrrole Derivatives

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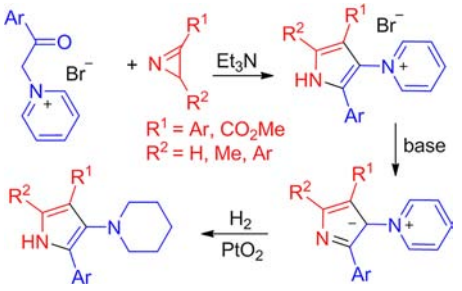
ABSTRACT



A flexible approach to unknown 1-(1*H*-pyrrol-3-yl)pyridinium salts with selective control of the substitution patterns, by the reaction of pyridinium ylides with 2*H*-azirines, is disclosed. 3-(Pyridinium-1-yl)pyrrolides, a new type of stable ylide, were prepared from these salts in high yields by treatment with base. Atmospheric-pressure hydrogenation of the ylides with Adams' catalyst lead to 1-(pyrrol-3-yl)piperidines in good yields.

Pyrrole is one of the most important simple heterocycles, whose structural unit is present in a large number of natural compounds, medical and material molecules.[1] By limiting ourselves to a short introduction it is impossible to reflect adequately the variety of chemistry and the value of pyrrole derivatives, so we will mention only recently published works in which the bioactivity of compounds containing 3-(pyridine-1-yl)pyrrole fragments were investigated, since compounds of this type are a subject of our research. The mentioned structural units are present in compounds which are antibacterial agents targeting DNA gyrase,[2] inhibitors of human DPP-4 for the treatment of type 2 diabetes,[3] NMDA receptor antagonists,[4] selective NK_1 antagonists,[5] and potent antagonists of VLA-4.[6] Although excellent preparative methods for the synthesis of substituted pyrroles have been developed,[1] it is still a great challenge to synthesize functionalized pyrroles from readily available and easily varied starting materials using a simple procedure. One such approach to the synthesis of pyrrole derivatives is based on the reactions of nucleophiles with 2*H*-azirines. The first example of reactions of 3-phenyl-2*H*-azirine with enolates leading to pyrrole derivatives was published by Sato.[7] 2*H*-Pyrroles were prepared in good yields from 2*H*-azirines and enolates from activated

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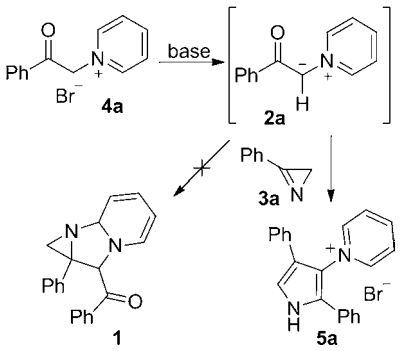
carbonyl compounds.[8] It was shown that enoles can also be used as nucleophiles in such reactions.[9] Enamines, another synthetic equivalent of enolate anions, react with substituted 2*H*-azirines to give a mixture of 2,3- and 3,4-dihydropyrroles which on acid treatment yields 1*H*-pyrrole-2-carboxylic acid derivatives.[10] Alkyl 2*H*-azirine-2-carboxylates react with acetylacetone or $Cu(acac)_2$ to give the corresponding 1*H*-pyrroles.[11] Tri- or tetra-substituted pyrroles were synthesized by reaction of 1,3-dicarbonyl compounds with 2*H*-azirine, which is itself generated in situ by thermolysis of vinyl azides.[11b,12] A selective synthesis of substituted pyrrole-2-phosphane oxides and -phosphonates from 2*H*-azirines and enolates from acetyl acetates and malonates was recently developed.[13] The reported reaction between stabilized phosphorus ylides and highly electrophilic dimethyl 2*H*-azirine-2,3-dicarboxylate afforded the corresponding pyrroles in low yield.[10a] Reactions of azirines with nitrogen ylides are, to the best of our knowledge, unknown to date.

Based on our research interest concerning the synthesis of nitrogenated heterocycles via nitrogen ylide reactions[14] and the chemistry of azirines[14b,d,e,i,15] we could envision the possibility of assembling a new heterocyclic system **1**, by 1,3-dipolar cycloaddition of pyridinium ylide **2a** to the C=N bond of 2*H*-azirine **3a**. But by serendipity we found that ylide **2a**, generated from salt **4a**, reacted with azirine **3a** as a nucleophile, disclosing a methodology for the synthesis of unknown 1-(1*H*-pyrrol-3-yl)pyridinium salts **5** (Scheme 1).

To study the scope of this approach we performed the reaction of salts **4a**–**c** containing both electron-donating and -withdrawing substituents on the benzoyl group,

Scheme 1



pycolinium **4d**, and isoquinolinium analogs **4e** with 3-mono- and 2,3-disubstituted azirines **3a**–**f** (Table 1). The reaction of salts **4** with azirines **3** in CH_2Cl_2 with Et_3N at rt gives after ~1 day the corresponding salts **5** in good yields. In boiling methylene chloride the reaction is completed about 10 times faster, but this variant of the procedure is less appropriate for thermally unstable azirines **3c,e,f**.

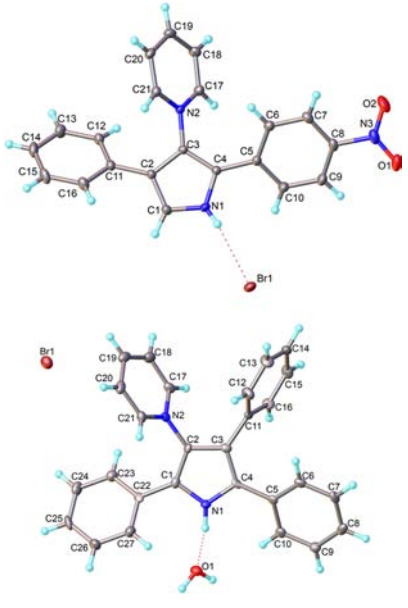


Figure 1. Molecular structure of compounds **5e,h**.

The reaction conditions and yields of tri- and tetrasubstituted pyrrole derivatives are presented in Table 1. The structures of compounds **5** were verified by ^1H, ^{13}C NMR, IR spectroscopy, HRMS, and elemental analysis. Structures of compounds **5e,f,h** were confirmed by X-ray analysis (Figure 1 and Supporting Information). Salts **5** are stable bright yellow crystalline compounds with high melting points. These hygroscopic substances are soluble in water and methanol and insoluble in diethyl ether, methylene chloride, and hexane.

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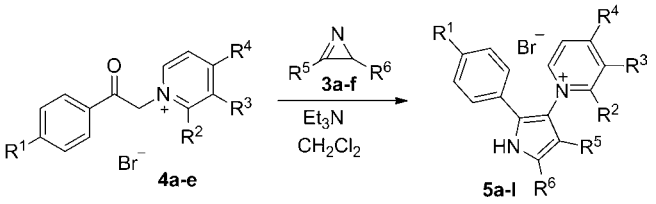
Table 1. Synthesis of 3-(1*H*-Pyrrol-3-yl)pyridinium Salts **5**

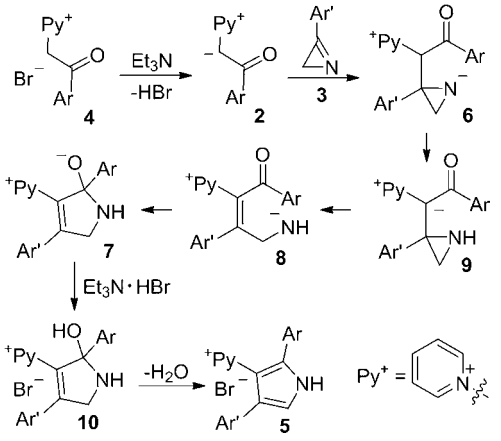


entry	R^1	R^2	R^3	R^4	R^5	R^6	salt **4**	azirine **3**	procedure,[a] *t* (h)	yield of **5** (%)
1	H	H	H	H	Ph	H	**a**	**a**	*A*(24)/*B*(2)	**a** (76/72)
2	H	H	H	H	4-BrC_6H_4	H	**a**	**b**	*A*(24)/*B*(2)	**b** (74/71)
3	H	H	H	H	4-$MeOC_6H_4$	H	**a**	**c**	*A*(24)	**c** (70)
4	MeO	H	H	H	Ph	H	**b**	**a**	*B*(2)	**d** (80)
5	NO_2	H	H	H	Ph	H	**c**	**a**	*B*(2.5)	**e** (85)
6	H	Me	H	H	Ph	H	**d**	**a**	*B*(3)	**f** (79)
7	H	H	$(CH{=}CH)_2$		Ph	H	**e**	**a**	*A*(24)	**g** (60)
8	H	H	H	H	Ph	Ph	**a**	**d**	*B*(3)	**h** (79)
9	MeO	H	H	H	Ph	Ph	**b**	**d**	*B*(2)	**i** (85)
10	NO_2	H	H	H	Ph	Ph	**c**	**d**	*B*(3)	**j** (71)
11	MeO	H	H	H	Ph	Me	**b**	**e**	*A*(24)	**k** (87)
12	MeO	H	H	H	CO_2Me	4-ClC_6H_4	**b**	**f**	*A*(24)	**l** (69)

[a] *A*: stirring at rt. *B*: reflux in CH_2Cl_2.

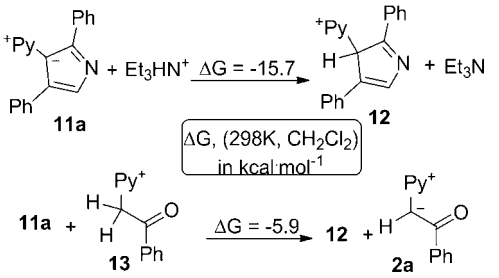
The probable mechanism for the formation of 1-(1*H*-pyrrol-3-yl)pyridinium salts **5** by the reaction of azirines **3** with ylides **2** is shown in Scheme 2.

Scheme 2



Further, we tried to generate a new type of pyridinium ylide, 3-(pyridinium-1-yl)pyrrolides **11**, by treating salts **5** with a base (Table 2). It was found that NaOH, KOH, and K_2CO_3 convert the salts **5** to ylides **11** practically quantitatively. The use of pyridine or Et_3N does not lead to the desirable result, due to the relatively high basicity of pyridinium-pyrrolides **11**. In particular, this follows from free energy parameters for isodesmic reactions (Scheme 3), obtained by DFT B3LYP/6-31G(d) calculations.[16] The high basicity of ylides **11** means that if they were intermediate for the formation of salts **5**, the reaction could proceed in an autocatalytic mode using only catalytic amounts of Et_3N. A special experiment showed, however, that under these conditions the reaction proceeds very slowly.

Scheme 3

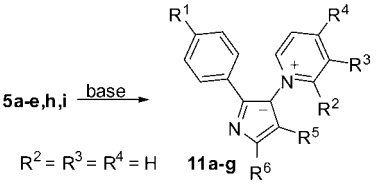


The structures of compounds **11** were verified by standard spectroscopic methods. There is a long-wave absorption band in the UV spectra of ylides **11** (λ 485−500 nm, ε = 300−500), which is responsible for the color of these compounds (from brick-red to dark-violet). It is easy to change the counterion in salts **5** via ylide **11**. For example, consecutive reactions of salt **5d** with KOH and then with an excess of hydrochloric acid leads to the chloride **14** in quantitative yield (Scheme 4).

On contact with air the ylides **11** react, in crystalline form or dissolved in methanol, with carbonic acid in the air to give the corresponding hydrocarbonates (Scheme 4). The structure of the hydrocarbonate **15**, prepared by keeping the ylide **11b** in air, was established by X-ray analysis (see Supporting Information).

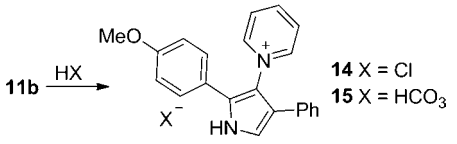
(16) The details of calculations will be published elsewhere.

Table 2. Synthesis of 3-(Pyridinium-1-yl)pyrrolides **11**



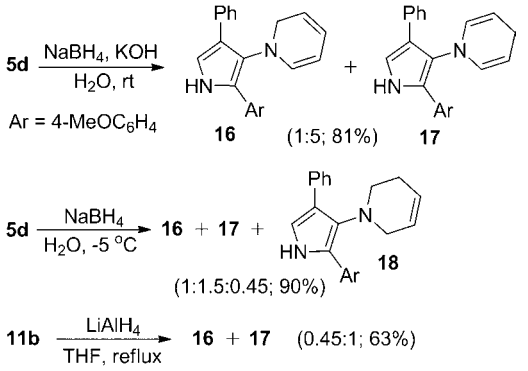
entry	R^1	R^5	R^6	**5**	yield of **11** (%)
1	H	Ph	H	**a**	**a** (98)
4	MeO	Ph	H	**d**	**b** (95)
5	NO_2	Ph	H	**e**	**c** (91)
2	H	4-BrC_6H_4	H	**b**	**d** (91)
3	H	4-$MeOC_6H_4$	H	**c**	**e** (92)
8	H	Ph	Ph	**h**	**f** (93)
9	MeO	Ph	Ph	**i**	**g** (96)

Scheme 4



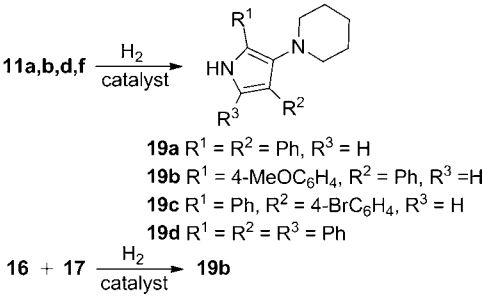
Because compounds with the fragment of 3-(piperidin-1-yl)pyrrole demonstrate a varied bioactivity[2−6] the reduction of salts **5** and ylides **11** were investigated. The reduction of salt **5d** or ylide **11d** by complex metal hydrides led to the mixtures of di- and tetrahydropyridine derivatives (Scheme 5) which were impossible to separate because of the very close R_f parameters and the instabilty under chromatography on SiO_2 or Al_2O_3.

Scheme 5



Catalytic hydrogenation at atmospheric pressure of 3-(pyridinium-1-yl)pyrrolides **11** or of the mixtures of dihydropyridines **16**,**17** lead to the corresponding 1-(pyrrol-3-yl)-piperidines **19** (Table 3). The best results (highest yield and the shortest reaction time) were obtained when the ylide **11b** is reduced with Adams' catalyst in methanol (entry 4). These conditions were used for the hydrogenation of ylides **11a,d,f** giving piperidines **19a,c,d** in good yields.

Table 3. Hydrogenation of 3-(Pyridinium-1-yl)pyrrolides **11**



entry	substrate	catalyst[a]	solvent	time (h)	yield of **19** (%)
1	**20** + **21**	PtO_2	EtOH	11	**b** (66)
2	**20** + **21**	10%Pt/C	EtOH	10	**b** (46)
3	**11b**	PtO_2	EtOH	6	**b** (51)
4	**11b**	PtO_2	MeOH	0.5	**b** (87)
5	**11b**	PtO_2 (5%)	MeOH	1.5	**b** (39)
6	**11b**	PtO_2 (3%)	MeOH	1.5	**b** (33)
7	**11b**	10%Pt/C	EtOH	5	**b** (37)
8	**11b**	10%Pt/C	MeOH	0.5	**b** (59)
9	**11b**	5%Pt/C	EtOH	2	**b** (49)
10	**11b**	5%Pt/C	MeOH	0.5	**b** (63)
11	**11b**	10%Pd/C	MeOH	22	0
12	**11a**	PtO_2	MeOH	0.5	**a** (84)
13	**11d**	PtO_2	MeOH	0.5	**c** (75)
14	**11f**	PtO_2	MeOH	0.5	**d** (89)

[a] Entries 1–4, 7–14: 10% w/w of catalyst.

In summary, a novel effective approach to the synthesis of unknown 1-(1*H*-pyrrol-3-yl)pyridinium salts by the reaction of pyridinium ylides with 2*H*-azirines was disclosed. 1-(1*H*-Pyrrol-3-yl)pyridinium salts can be easily tranformed into 3-(pyridinium-1-yl)pyrrolides, a new type of stable ylide. Catalytic atmospheric-pressure hydrogenation of 3-(pyridinium-1-yl)pyrrolides with Adams' catalyst lead to 1-(pyrrol-3-yl)piperidines in good yields. Further applications of the suggested methodology are currently under investigation.

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Supporting Information Available. Experimental procedures, spectroscopic data for all new compounds, CIF files for **5e,f,h** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.