Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1395–1398
Tetrahedron Letters

Novel one pot synthesis of azolo[1,5-*a*]pyridines from Viehe's salts

Alexander S. Kiselyov*

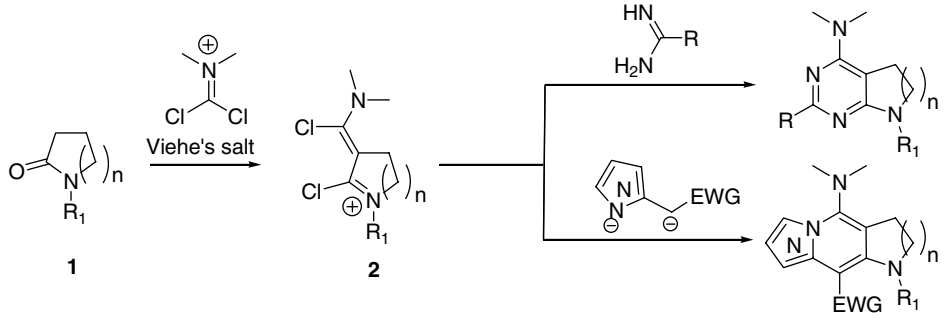
Small Molecule Drug Discovery, Chemical Diversity, 11558 Sorrento Valley Road, San Diego, CA 92121, USA

Received 12 December 2005; revised 14 December 2005; accepted 19 December 2005

Abstract—We have developed a practical procedure for the synthesis of polyfunctional azolo[1,5-*a*]pyridines via the reactive species generated in situ from *N*-substituted lactams and Viehe's salt. The reaction is regioselective with respect to the nucleophilic addition of bis-anions derived from methyl azolyl acetates. The described protocol allowed for the introduction of three elements of diversity into the targeted molecules, including substituents originating from the (i) nucleophile input, (ii) lactam ring, and (iii) nucleophilic aromatic displacement (S_NAr) of the NMe_2 group with amines. A short reaction sequence, good yields of title compounds (44–69%), as well as their ready isolation, and purification are the distinct advantages of the reported protocol.

Chemistries of Viehe's salt offer a facile access to a diverse array of products. These include the derivatives of 4-pyrone,[1] 2-pyrone,[2] pyrimidine,[3] 1,3-oxadiazin-6-one,[4] thiazole,[5] pyrazole,[6] various fused heterocycles,[7] and non-aromatic species.[8] Recently, a series of polysubstituted pyrimidines were synthesized using the reaction of bis-electrophilic species **2** generated from Viehe's salts and lactams **1** with amidines and guanidines (Scheme 1).[9] This reaction sequence allowed for the introduction of three elements of diversity into the resultant molecules, including substituents originating from the (i) nucleophile input, (ii) lactam ring, and (iii) nucleophilic aromatic displacement (S_NAr) of the NMe_2 group.[10] In this letter, we further extended this protocol to access a series of azolo[1,5-*a*]pyridines via a novel one-pot reaction sequence (Scheme 1).

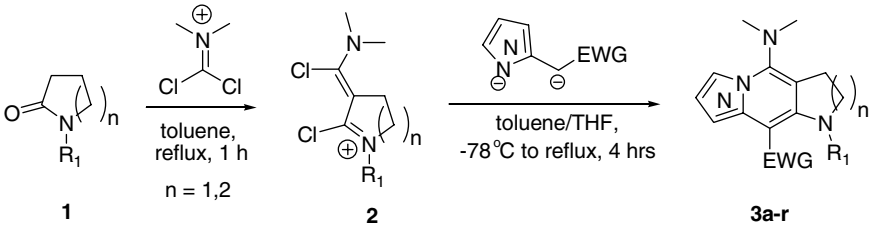
In the initial study, we synthesized a set of the targeted heterocycles with varying R_1 and fused azolyl substituents. Three commercially available *N*-substituted 2-pyrrolidinones **1a–c** (R_1 = Me, cyclohexyl, and Ph) were selected for the preparation of **2**. These were subsequently reacted with bis-anions derived from methyl azolyl acetates. The results of these experiments are summarized below (Scheme 2).[11] Targeted molecules were conveniently isolated in analytically pure form by trituration of the concentrated reaction mixtures with cold Et_2O followed by recrystallization of the resulting solid residue from EtOH. Analysis of the reaction mixtures (LC MS and ^1H NMR) suggested that the nucleophilic addition of bis-anions proceeds regioselectively as only single regioisomer **3** was detected and isolated.[12] The described transformations one likely to proceed



Scheme 1.

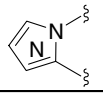
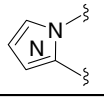
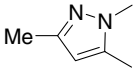
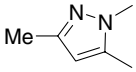
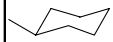
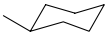
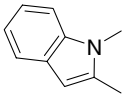
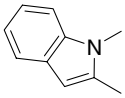
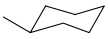
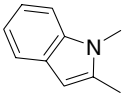
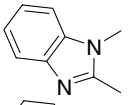
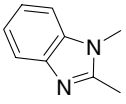
Keywords: Azolo[1,5-*a*]pyridines; Iminium salts; Viehe's salt; Lactams; Azolyl acetates; Condensations.
* Tel.: +1 858 794 4860; fax: +1 858 794 4931; e-mail: ask@chemdiv.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.103



1 2 3a-r

Yields[a] of pyrimidines **3a-r**

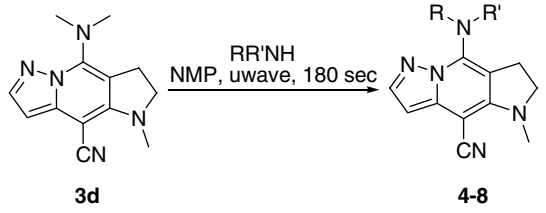
	Compound, **3**						Compound, **3**					
	n	R_1		EWG	Yield, %		n	R_1		EWG	Yield, %
a	1	Me		COOMe	44	**j**	2	Me		COOMe	46
b	1	Me		COOMe	51	**k**	2			CN	58
c	1			COOMe	57	**l**	2	Me		COOMe	53
d	1	Me		CN	56	**m**	2	Ph		COOMe	69
e	1	Ph		COOMe	62	**n**	1	Me		COOMe	68
f	1	Me		CN	47	**o**	2	Me		COOMe	44
g	1			COOMe	54	**p**	2	Ph		CN	63
h	1	Ph		COOMe	66	**q**	1	Me		COOMe	61
i	2	Me		COOMe	49	**r**	1	Me		COOMe	55

[a]Yields refer to isolated analytically pure compounds.

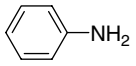
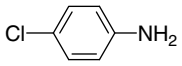
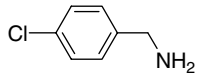
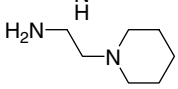
Scheme 2.

via the initial formation of the respective dichloro iminium species **2** that undergo nucleophilic attack by the *C*-atom of 1,3-dianions. This event is followed by cyclization and aromatization steps to yield the observed polysubstituted azolo[1,5-*a*]pyridines **3a**–**r**.

The nature of neither azolyl acetates nor lactams **1** significantly affected the outcome of the reaction (for example, compare yields for **3a** and **3i**, **3h** and **3m**, Scheme 2). *N*-Methyl substituted lactams furnished somewhat lower yields of the targeted heterocycles **3** (Scheme 2), presumably due to the hydrolytic instability of the respective iminium intermediate **2** under the reaction conditions. Optimized reaction conditions include application of dry THF/toluene or dioxane/toluene as solvents. Use of alternative solvent step including freshly distilled dry DMF, dimethoxyethane, or *N*-methylpyrrolidone (NMP) afforded somewhat lower yields of the targeted products (by ca. 10–15%). The nature of base used for deprotonation did not affect the outcome of the condensation. For example, LDA, Li(morpholide), NaHMDS, and KHMDS resulted in comparable yields



3d **4-8**

Product	RR'NH	Yield, %[a]
4		52
5		47
6		68
7		71
8		65

[a]Yields refer to isolated, analytically pure compounds.

Scheme 3.

of **3**, as evidenced by the LC MS analysis of the crude reaction mixtures. In addition to the targeted molecules **3a**–**r** the reaction mixtures also contained products of self-condensation of bis-anions (ca. 25–30%) and high molecular weight products. Additional quantities of **3a**–**r** (ca. 5–10%) could be isolated from the reaction mixtures by flash chromatography (Silicagel, eluent: hexanes/EtOAc, 2:1).

The described protocol was further extended to the synthesis of fused tricyclic systems **3n**–**r** (44–68% yields) by reaction of the intermediate **2** with dianions derived from 2-indole- and 2-benzimidazole methyl acetates (Scheme 2). Further, azolo[1,5-*a*]pyridine **3d** was reacted with a series of amines (Scheme 3) under microwave irradiation in dry NMP at 140 °C to furnish products of formal S_NAr of the NMe_2 group **4**–**8** in 47–71% yields (Scheme 3).[13]

In summary, we have developed a practical procedure for the synthesis of polyfunctional azolo[1,5-*a*]pyridines via the reactive species generated in situ from *N*-substituted lactams and Viehe's salt. The reaction is regiospecific with respect to the nucleophilic addition of bis-anions derived from methyl azolyl acetates. The described protocol allowed for the introduction of three elements of diversity into the targeted molecules, including substituents originating from the (i) nucleophile input, (ii) lactam ring, and (iii) nucleophilic aromatic displacement (S_NAr) of the NMe_2 group with amines. A short reaction sequence, good yields of title compounds (44–69%), as well as their ready isolation, and purification are the distinct advantages of the reported protocol.

References and notes

1. (a) Morris, J.; Wishka, D. G.; Luke, G. P.; Judge, T. M.; Gammill, R. B. *Tetrahedron* **1997**, *53*, 11211–11222; (b) Morris, J.; Luke, G. P.; Wishka, D. G. *J. Org. Chem.* **1996**, *61*, 3218–3220.
2. Bouvy, D.; Janousek, Z.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1993**, *102*, 129–140.
3. (a) Neidlein, R.; Wang, Z. *Synth. Commun.* **1997**, *27*, 1223–1235; (b) Wang, Z.; Neidlein, R. *Heterocycles* **1998**, *48*, 1923–1930; (c) Lockhart, C. C.; Sowell, J. W., Sr. *J. Heterocycl. Chem.* **1996**, *33*, 659–661.
4. (a) Decock-Plancquaert, M.-A.; Evariste, F.; Guillot, N.; Janousek, Z.; Maliverney, C.; Merenyi, R.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1992**, *101*, 313–321; (b) Neidlein, R.; Meffert, P.; Sui, Z. *Synthesis* **1992**, 443–446; (c) Neidlein, R.; Sui, Z. *Synthesis* **1990**, 959–961.
5. Maliverney, C.; Merenyi, R.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1990**, *99*, 941–949.
6. (a) Van Vyve, T.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 79; (b) De Voghel, G. J.; Eggerichs, T. L.; Janousek, Z.; Viehe, H. G. *J. Org. Chem.* **1974**, *39*, 1233; (c) Van Vyve, T.; Viehe, H. G. *Angew. Chem.* **1974**, *86*, 45; (d) Hervens, F.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 405.
7. For the synthesis of fused heterocycles using Viehe's salt, see: (a) Quintela, J. M.; Moreira, M. J.; Peinador, C. *Tetrahedron* **1996**, *52*, 3037–3048; (b) Quntela, J. M.; Veiga, M. C.; Peinador, C.; Gonzalez, L. *Heterocycles* **1997**, 1733–1743; (c) Peinador, C.; Quintela, J. M.; Moreira, M. J. *Tetrahedron* **1997**, *53*, 8269–8272; (d) Quintela, J. M.; Peinador, C. *Tetrahedron* **1996**, *52*, 10497–10506; (e) Player, M. R.; Sowell, J. W., Sr. *J. Heterocycl. Chem.* **1995**, *32*, 1537–1540; (f) Quintela, J. M.; Peinador, C.; Moreira, M. J. *Tetrahedron* **1995**, *51*, 5901–5912; (g) Kokel, B. *J. Heterocycl. Chem.* **1994**, *31*, 845–855; (h) Kokel, B. *J. Heterocycl. Chem.* **1994**, *31*, 1185–1192.
8. (a) Schlama, T.; Gouverneur, V.; Valleix, A.; Greiner, A.; Toupet, L.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 4200–4202; (b) Bouvy, D.; Janousek, Z.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1993**, *102*, 129–140; (c) Tinant, B.; Declercq, J.-P.; Bouvy, D.; Janousek, Z.; Viehe, H. G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 911–915; (d) Vovk, M. V.; Bratenko, M. K.; Samarai, L. I. *Ukr. Khim. Z.* **1991**, *57*, 431–432; (e) Guillot, N.; Janousek, M. B.; Viehe, H. G. *Synth. Commun.* **1989**, *19*, 2825.
9. Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 1177.
10. Vorbruggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117.
11. *Experimental procedure:* 1.5 mmol of Viehe's salt (Aldrich) was added to a vigorously stirred solution of 1 mmol of lactam in dry degassed toluene (15 mL) at room temperature under Ar. The heterogeneous dark yellow mixture was slowly warmed up to 80 °C (30 min), and the resulting mixture was stirred at this temperature for an additional 1.5 h. The dark-red mixture was quickly filtered under

argon blanket and cooled down to −70 °C. Separately, a solution of the respective methyl azolyl acetate (1 mM) in dry THF or dioxane (5 mL) was treated with freshly prepared LDA (2.5 mM) in the same solvent (5 mL) at −78 °C under Ar. The resulting pale yellow mixture was slowly (5–10 min) added via cannula to the toluene solution of **2** at 0 °C. The reaction mixture was slowly brought to rt (20 min) and, subsequently to reflux (20 min). Further, it was refluxed for additional 3–4 h. The mixture was then concentrated to ca. 10 mL on rotavap, diluted with EtOAc (50 mL), the organic extract was washed twice with brine (30 mL), dried over Na_2SO_4, concentrated to ca. 15 mL, cooled down in the freezer, and triturated with cold ether. The resulting crystals were collected, washed with ether, recrystallized from EtOH, and dried in vacuo to yield analytically pure azolo[1,5-*a*]-pyridines in a 44–69% yields. Additional quantities of **3a**–**r** (ca. 5–10%) could be isolated from the reaction mixtures by flash chromatography (Silicagel, eluent: hexanes/EtOAc, 2:1).

Analytical data for representative compounds:

Compound **3a**: 44% yield, mp 227–229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.54 (s, 3H, N–Me), 2.66 (s, 6H, NMe_2), 2.84 (m, 2H), 3.56 (m, 2H), 3.92 (s, 3H, COOMe), 6.54 (d, $J = 5.6$ Hz, 1H), 7.95 (d, $J = 5.6$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.8, 36.9, 41.1, 51.4, 54.6, 96.2, 100.4, 109.3, 133.5, 134.8, 155.7, 163.0, 167.1. ESI MS: (M+1) 275, (M−1) 273; HR ESI MS: Exact mass calcd for $C_{14}H_{13}N_4O_2$: 274.1430, found: 274.1422. Elemental analysis, calcd for $C_{14}H_{13}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.09; H, 6.47; N, 20.27.

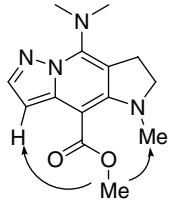
Compound **3h**: 66% yield, mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.69 (s, 6H, NMe_2), 2.85 (m, 2H), 3.64 (m, 2H), 3.92 (s, 3H, COOMe), 6.61 (d, $J = 7.2$ Hz, 2H), 6.69 (m, 1H), 7.02 (m, 2H), 7.56 (d, $J = 4.8$ Hz, 1H), 7.79 (d, $J = 4.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.9, 40.7, 50.2, 51.7, 98.8, 108.3, 112.7, 115.0, 117.6, 125.7, 128.4, 141.8, 148.2, 157.3, 162.5, 166.5. ESI MS: (M+1) 337, (M−1) 335; HR ESI MS: Exact mass calcd for $C_{19}H_{20}N_4O_2$: 336.1586, found: 336.1578. Elemental analysis, calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.66. Found: C, 67.58; H, 6.14; N, 16.21.

Compound **3l**: 53% yield, mp 235–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92 (m, 2H), 2.51 (s, 3H, N–Me), 2.60 (s, 6H, NMe_2), 2.75 (m, 2H), 3.18 (m, 2H), 3.90 (s, 3H, COOMe), 7.54 (d, $J = 4.8$ Hz, 1H), 7.81 (d, $J = 4.8$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8, 21.1, 38.2, 40.4, 50.1, 51.2, 99.6, 100.1, 116.2, 125.4, 144.9, 155.3, 162.0, 168.5. ESI MS: (M+1) 289, (M−1) 287; HR ESI MS: Exact mass calcd for $C_{15}H_{20}N_4O_2$: 288.1586, found: 288.1581. Elemental analysis, calcd for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.23; H, 7.11; N, 19.21.

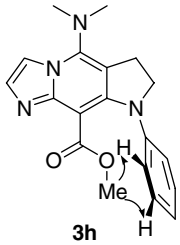
Compound **3n**: 68% yield, mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44 (s, 3H, N–Me), 2.55 (s, 6H, NMe_2), 2.72 (m, 2H), 3.25 (m, 2H), 3.92 (s, 3H, COOMe), 6.35 (s, 1H), 7.05 (m, 1H), 7.12 (m, 1H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.51 (d, $J = 7.2$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.2, 36.4, 39.9, 51.3, 55.8, 94.5, 96.2, 98.8, 110.7, 113.5, 119.4, 119.8, 120.5, 122.3, 128.6, 137.5, 139.7, 165.7. ESI MS: (M+1) 324, (M−1) 322; HR ESI MS: Exact mass calcd for $C_{19}H_{21}N_3O_2$: 323.1634, found: 323.1625. Elemental analysis, calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.36; H, 6.38; N, 12.81.

Compound **5**: 47% yield, mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.49 (s, 3H, N–Me), 2.84 (m, 2H), 3.41 (m, 2H), 5.12 (br s, exch D_2O, 1H, NH), 6.44 (d, $J = 5.6$ Hz, 1H), 6.55 (d, $J = 7.8$ Hz, 2H), 6.98 (d, $J = 7.8$ Hz, 2H), 7.75 (d, $J = 5.6$ Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.4, 36.8, 55.6, 87.6, 95.4, 110.9, 117.3, 118.3, 123.7, 129.6, 132.5, 134.0, 141.8, 160.5, 166.7. ESI MS: (M+1) 325, (M−1) 323; HR ESI MS: Exact mass calcd for $C_{17}H_{14}ClN_5$ 323.0938, found: 323.0934. Elemental analysis, calcd for $C_{17}H_{14}ClN_5$: C, 63.06; H, 4.36; N, 21.63. Found: C, 62.87; H, 4.19; N, 21.48.

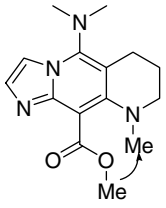
12. Significant NOE's for the selected compounds.



3a



3h



3l

13. Microwave heating of **3d** with amines in NMP for 180 s was found to yield better yields of the targeted amines **4**–**8** (by ca. 20–30%, as evidenced by LC MS analyses of the crude reaction mixtures) when compared to a conventional heating of the reaction components in *i*-PrOH, dioxane, or DMF. However, under these conditions, reactions of methyl esters **3a**–**c** with amines resulted in significant formation of the respective amides (ca. 30–50% yields), along with S_NAr of the NMe_2 group. The yields of amides were reduced to ca. 10–15% by prolonged heating of the reaction components (48–72 h) at 70 °C in NMP. Under these conditions the conversion of **3a**–**c** was 60–70%, whereas the yields of the respective amines were 80–90%.