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Furan ring opening–pyrrole ring closure. A simple route to 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-ones

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ABSTRACT

We report here an application of a furan ring opening-Paal–Knorr pyrrole synthesis sequence for the transformation of furfurylamines into 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-ones.

Pyrrole derivatives represent a very important class of heterocyclic compounds.[1] Among them, pyrroles annulated to other heterocycles via a C–N bond can be highlighted due to the broad spectrum of their bioactivity. The antitumor and antibiotic agent, mitomycin is a pyrrolo[1,2-*a*]indole derivative, whilst the anti-HIV agent castanospermine has an indolizidine scaffold; *Erythrina* alkaloids belong to pyrrolo[2,1-*a*]isoquinoline family; and the pyrrolo[1,2-*b*]isoquinoline fragment is present in *Amaryllidaceae* alkaloids. Aptazapine, bretazenil, ketorolac, and other drugs also contain a pyrrole moiety, the C–N bond of which is annulated to another ring(s).

All syntheses of these compounds can be divided into three main groups: (a) cyclizations of functionalized pyrroles affording annulated azaheterocycles; (b) formation of pyrrole rings in compounds containing an azaheterocycle; (c) simultaneous formation of both rings. The third group includes recyclization of appropriately substituted furans. The last approach was utilized to prepare 5-alkyl-2-aminomethylpyrroles,[2] indoles,[3] isoindoles,[4] pyrrolo[2,3-*d*]pyridazines,[5] pyrrolo[1,2-*a*][1,4]diazepines,[6] pyrrolo[1,2-*d*][1,4]diazepines,[7] and other pyrrole ring-containing polycyclic systems.[8] In continuation of our program on the synthesis of various heterocycles based on furan recyclizations,[9] we applied this method for the preparation of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.[10,11] This fragment is present in natural compounds (e.g., the antibacterial longamide A, the antiprotozoal longamide B, cytotoxic agelastatin A, and palau'amine, etc.), as well as in synthetic drugs, such as ranirestat which is utilized for the treatment of diabetic neuropathy (Fig 1).[12]

Relying on our previous experience,[2,6,7] we designed a route to 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-ones **1** as depicted in Scheme 1. The pyrrolo[1,2-*a*]pyrazine core can be obtained by an acid-catalyzed recyclization of *N*-furfurylamides of α-amino acids

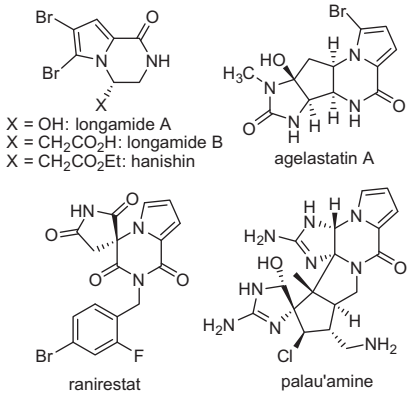

Fig. 1. Several bioactive 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.

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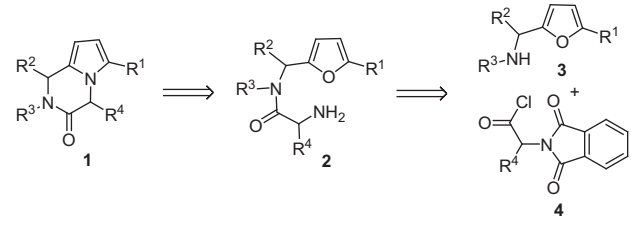
2, which, in turn, can be prepared by acylation of furfurylamines **3** with α-phthalimidoacyl chlorides **4**.

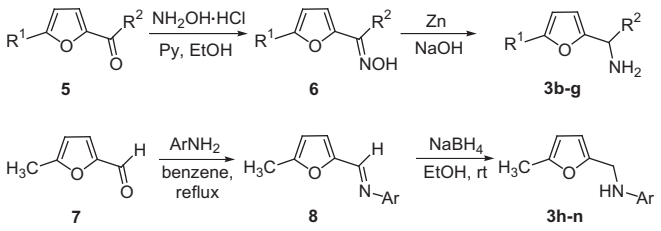
To realize this approach, we prepared a number of furfurylamines **3** bearing various substituents on nitrogen, C5, and the α-C atoms (Scheme 2).[13,14]

The acylation of **3a**–**n** with α-phthalimidoacyl chlorides **4** afforded the corresponding *N*-furfurylamides **9** in good to excellent yields (Scheme 3, Table 1). Removal of the phthaloyl group under treatment with hydrazine hydrate produced amines **2**, which underwent acid-catalyzed transformation into tetrahydropyrrolo[1,2-*a*]pyrazines **1** via a furan ring opening-Paal–Knorr cyclization sequence.[15–17]

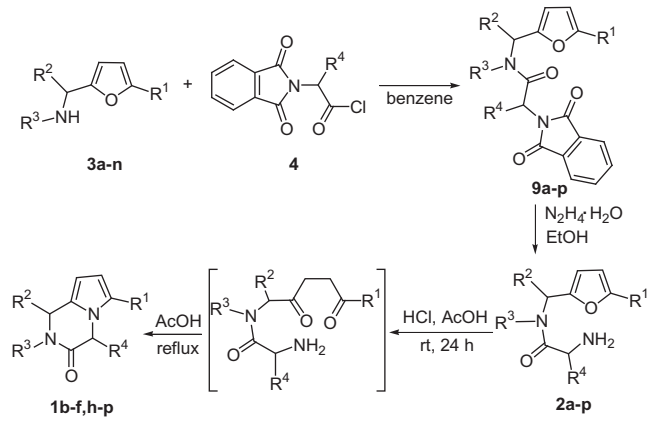
Deprotection of **9** followed by recyclization of **2** into **1** proceeded with reasonable yields with a few exceptions. Namely, all attempts to recyclize **2a** failed due to the well-known polymerization of 5-unsubstituted furans under acidic conditions. Moreover, we need to point out that introduction of a substituent at the α-position of furfurylamine was accompanied by a significant decrease in the yield of the recyclization product (entries **e-g**, Table 1). This effect was earlier demonstrated for various furan recyclizations and was rationalized by the increased stability of the furfuryl cation which can eliminate under the reaction conditions via the amide group protonation.[6a] At the same time, both N-unsubstituted and N-substituted pyrrolopyrazines **1** were efficiently formed by this reaction. Moreover, quite different functional groups on the arene substituent were compatible with the reaction conditions. Similarly, not only glycine-derived **4**, but also other amino acid derivatives could participate in the discussed transformation (entries **o** and **p** in Table 1).[11]



Scheme 1. Retrosynthetic analysis of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.



Scheme 2. Synthesis of furfurylamines **3b**–**n**.



Scheme 3. Transformation of furfurylamines **3** into 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines.

Table 1
Synthesis of *N*-furfuryl-2-phthalimidoamides **9** and 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **1**

Entry	R^1	R^2	R^3	R^4	Yield[a] (%)	
					9	**1**
a	H	H	H	H	79	—[b]
b	Me	H	H	H	82	67
c	Et	H	H	H	90	65
d	*t*-Bu	H	H	H	88	73
e	Me	Me	H	H	82	32
f	Me	Ph	H	H	80	15
g	Me	3,4-$(MeO)_2C_6H_3$	H	H	88	—[b]
h	Me	H	2-FC_6H_4	H	81	74
i	Me	H	4-MeC_6H_4	H	79	69
j	Me	H	4-$MeOC_6H_4$	H	84	62
k	Me	H	4-ClC_6H_4	H	91	69
l	Me	H	4-FC_6H_4	H	95	67
m	Me	H	4-$F_3CC_6H_4$	H	76	70
n	Me	H	3-$F_3CC_6H_4$	H	85	59
o	Me	H	H	Me	82	65
p	Me	H	H	*i*-Pr	84	57

[a] Isolated yield.
[b] Significant polymerization precluded isolation of the target products.

To conclude, we have developed a simple and efficient approach to differently substituted 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-ones. Easy functionalization of these compounds allows for preparation of pyrrolopyrazines with other substitution patterns. The scope of the applications and restrictions of the method are currently under investigation.

Acknowledgments

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References and notes

1. (a)*The Chemistry of Heterocyclic Compounds: Pyrroles. Part 1*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, p 742; (b)*The Chemistry of Heterocyclic Compounds: Pyrroles. Part 2*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, p 628; (c) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421.
2. Butin, A. V.; Nevolina, T. A.; Shcherbinin, V. A.; Uchuskin, M. G.; Serdyuk, O. V.; Trushkov, I. V. *Synthesis* **2010**, 2969–2978.
3. (a) Yin, B.; Cai, C.; Zeng, G.; Zhang, R.; Li, X.; Jiang, H. *Org. Lett.* **2012**, *14*, 1098–1101; (b) Petronijevic, F.; Timmons, C.; Cuzzupe, A.; Wipf, P. *Chem. Commun.* **2009**, 104–106; (c) Butin, A. V.; Smirnov, S. K.; Stroganova, T. A.; Bender, W.; Krapivin, G. D. *Tetrahedron* **2007**, *63*, 474–491; (d) Butin, A. V.; Smirnov, S. K. *Tetrahedron Lett.* **2005**, *46*, 8443–8445; (e) Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 189–191.
4. (a) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672–6678; (b) Hashmi, A. S. K.; Schaefer, S.; Bats, J. W.; Frey, W.; Rominger, F. *Eur. J. Org. Chem.* **2008**, 4891–4899; (c) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554.
5. El Kaim, L.; Grimaud, L.; Wagschal, S. *Chem. Commun.* **2011**, *47*, 1887–1889.
6. (a) Butin, A. V.; Nevolina, T. A.; Shcherbinin, V. A.; Trushkov, I. V.; Cheshkov, D. A.; Krapivin, G. D. *Org. Biomol. Chem.* **2010**, *8*, 3316–3327; (b) Stroganova, T. A.; Butin, A. V.; Vasilin, V. K.; Nevolina, T. A.; Krapivin, G. D. *Synlett* **2007**, 1106–1108.
7. (a) Nevolina, T. A.; Shcherbinin, V. A.; Serdyuk, O. V.; Butin, A. V. *Synthesis* **2011**, 3547–3551; (b) Shcherbinin, V. A.; Nevolina, T. A.; Butin, A. V. *Chem. Heterocycl. Compd.* **2010**, *46*, 1542–1544.
8. (a) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704–7707; (b) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782–3785; (c) Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855–2875; (d) Butin, A. V.; Tsiunchik, F. A.; Abaev, V.

T.; Zavodnik, V. E. *Synlett* **2008**, 1145–1148; (e) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279–282.

9. (a) Uchuskin, M. G.; Pilipenko, A. S.; Serdyuk, O. V.; Trushkov, I. V.; Butin, A. V. *Org. Biomol. Chem.* **2012**, *10*, 7262–7265; (b) Uchuskin, M. G.; Molodtsova, N. V.; Abaev, V. T.; Trushkov, I. V.; Butin, A. V. *Tetrahedron* **2012**, *68*, 4252–4258; (c) Pilipenko, A. S.; Mel'chin, V. V.; Trushkov, I. V.; Cheshkov, D. A.; Butin, A. V. *Tetrahedron* **2012**, *68*, 619–627; (d) Butin, A. V.; Tsiunchik, F. A.; Kostyukova, O. N.; Uchuskin, M. G.; Trushkov, I. V. *Synthesis* **2011**, 2629–2638; (e) Butin, A. V.; Tsiunchik, F. A.; Kostyukova, O. N.; Trushkov, I. V. *Chem. Heterocycl. Compd.* **2010**, *46*, 1539–1541; (f) Butin, A. V.; Uchuskin, M. G.; Pilipenko, A. S.; Tsiunchik, F. A.; Cheshkov, D. A.; Trushkov, I. V. *Eur. J. Org. Chem.* **2010**, 920–926.
10. For examples of pyrrolopyrazine syntheses, see: (a) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *14*, 1062–1065; (b) Hewlett, N. M.; Tepe, J. J. *Org. Lett.* **2011**, *13*, 4550–4553; (c) He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490–4493; (d) Gualandi, A.; Cerisoli, L.; Monari, M.; Savoia, D. *Synthesis* **2011**, 909–918; (e) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. *Chem. Eur. J.* **2010**, *16*, 12462–12473; (f) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800–15807; (g) Mukherjee, S.; Sivappa, R.; Yousufuddin, M.; Lovely, C. J. *Org. Lett.* **2010**, *12*, 4940–4943; (h) Imaoka, T.; Akimoto, T.; Iwamoto, O.; Nagasawa, K. *Chem. Asian J.* **2010**, *5*, 1810–1816; (i) Trost, B. M.; Osipov, M.; Dong, G. *Org. Lett.* **2010**, *12*, 1276–1279.
11. When this manuscript was in preparation, Batra and co-workers reported the analogous preparation of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines from furfurylamines and optically active α-amino acids, see: Bhowmik, S.; Kumar, A. K. S.; Batra, S. *Tetrahedron Lett.* **2013**, *54*, 2251–2254.
12. For examples of the bioactivity of 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines, see: (a) Scala, F.; Fattorusso, E.; Menna, M.; Taglialatela-Scafati, O.; Tierney, M.; Kaiser, M.; Tasdemir, D. *Mar. Drugs* **2010**, *8*, 2162–2174; (b) Tilvi, S.; Moriou, C.; Martin, M.-T.; Gallard, J.-F.; Sorres, J.; Patel, K.; Petek, S.; Debitus, C.; Ermolenko, L.; Al-Mourabit, A. *J. Nat. Prod.* **2010**, *73*, 720–723; (c) Zhu, B.; Marinelli, B. A.; Goldschmidt, R.; Foleno, B. D.; Hilliard, J. J.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4933–4936; (d) Wiscount, C. M.; Williams, P. D.; Tran, L. O.; Embrey, M. W.; Fisher, T. E.; Sherman, V.; Homnick, C. F.; Staas, D. D.; Lyle, T. A.; Wai, J. S.; Vacca, J. P.; Wang, Z. Q.; Felock, P. J.; Stillmock, K. A.; Witmer, M. V.; Miller, M. D.; Hazuda, D. J.; Day, A. M.; Gabryelski, L. J.; Ecto, L. T.; Schleif, W. A.; DiStefano, D. J.; Kochansky, C. J.; Anari, M. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4581–4583; (e) Kurono, M.; Itogawa, A.; Noguchi, H.; Sanjoba, M. *J. Pharm. Sci.* **2008**, *97*, 1468–1483.
13. Furfurylamine **3a** is commercially available. Furfurylamines **3b–g** were synthesized from the corresponding oximes by the published method: Kuo, Y.-H.; Shih, K.-S. *Chem. Pharm. Bull.* **1991**, *39*, 181–183; *N*-Furfurylanilines **3h–n** were obtained using a modified[10] literature procedure, see: Sarang, P. S.; Yadav, A. A.; Patil, P. S.; Krishna, U. M.; Trivedi, G. K.; Salunkhe, M. M. *Synthesis* **2007**, 1091–1095.
14. *General procedure for the synthesis of N-arylfurfurylamines **3h–n***. A solution of 5-methylfurfural (**7**) (5.0 g, 45.45 mmol) and aniline (41.3 mmol) in benzene (50 mL) was refluxed using a Dean-Stark trap for 2 h, and then evaporated to dryness. The obtained imine **8** was dissolved in EtOH (30 mL) and treated portionwise with $NaBH_4$ (1.56 g, 41.3 mmol). The mixture was stirred for 1–2 h until completion (TLC monitoring). The reaction was poured into H_2O (100 mL), neutralized with 10% AcOH until pH 7, and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic fractions were dried with Na_2SO_4 and evaporated under reduced pressure to dryness. The residue was passed through a pad of Al_2O_3 using petroleum ether (**3h–j**, **l–n**) or benzene–petroleum ether (**3k**) mixture as the eluent. Amine **3k** was recrystallized from petroleum ether below 0 °C (86% yield). Other amines were used in the following transformations without additional purification (**3h**, 82%; **3i**, 91%; **3j**, 92%; **3l**, 84%; **3m**, 92%; **3n**, 80% yield).
15. *General procedure for the synthesis of amides **9***. A solution of α-phthalimidoacyl chloride (**4**) (6.0 g, 26.9 mmol) in benzene (50 mL) was added dropwise over 30 min to a solution of amine **3** (24.4 mmol) in benzene (50 mL). The mixture was stirred for 1 h at room temperature (TLC monitoring), then saturated aq $NaHCO_3$ solution was added, and the mixture was stirred vigorously for 30 min. The resulting precipitate was removed by filtration and the organic layer was separated and the aqueous phase extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (30 mL), dried with Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was combined with the obtained precipitate after treatment of the reaction mixture with $NaHCO_3$ and passed through a pad of silica gel or Al_2O_3 followed by recrystallization.
16. *General procedure for the preparation of N-furfuryl-α-aminoacylamides **2***. Hydrazine hydrate (6.0 mL) was added to a solution of amide **9** (6.0 g) in EtOH (30 mL). The reaction mixture was refluxed for 5 min (TLC monitoring) and cooled to room temperature. The resulting precipitate was removed by filtration and washed with cold EtOH. The mother liquor was evaporated to dryness under reduced pressure, treated with H_2O (100 mL), and carefully extracted with Et_2O (5 × 30 mL). The organic phases were combined, dried with Na_2SO_4 and evaporated to dryness under reduced pressure. Compounds **2g**, **2m**, and **2n** were recrystallized from EtOH, petroleum ether–CH_2Cl_2 mixture, and from petroleum ether below 0 °C, respectively. Other amines **2** were used for further transformations without additional purification.
17. *General procedure for the recyclization of aminofurans **2** into 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazin-3-ones **1***. A mixture of amine **2** (1.0 g), glacial AcOH (20 mL), and concd HCl (3 mL) was stirred for 24 h at room temperature (TLC monitoring). Then $NaHCO_3$ (3.0 g) was added portionwise, the reaction mixture was refluxed for 3 min, poured into H_2O (100 mL) and neutralized to pH 7. The formed precipitate was filtered, washed with H_2O, dried, and passed through a pad of silica gel or Al_2O_3. The solvent was evaporated to dryness and the product recrystallized.