Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2015, **25**, 329–331
Mendeleev Communications

One-pot synthesis of 1-arylmethylidene-1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazines and 1-arylmethylidene-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]-quinazolines from 5-arylalk-4-ynals and *o*-aminobenzylic alcohol/amine

Valentin D. Gvozdev,* Konstantin N. Shavrin, Mikhail P. Egorov and Oleg M. Nefedov

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: vgvozdev2006@yandex.ru

DOI: 10.1016/j.mencom.2015.09.002

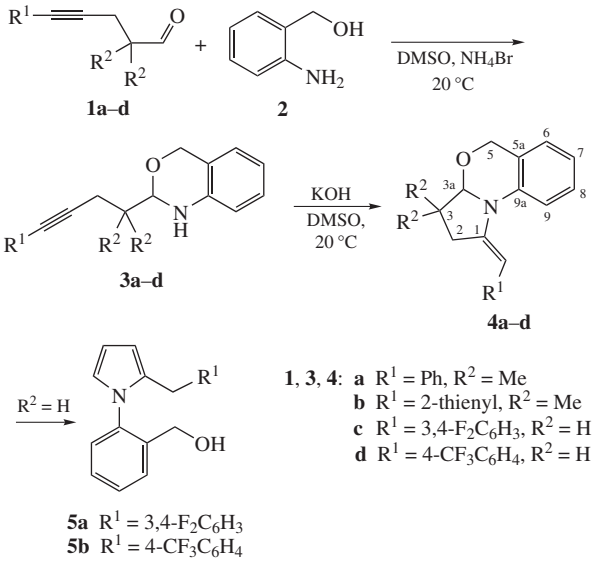
Cyclization of 5-arylalk-4-ynals with *o*-aminobenzylamine or *o*-aminobenzyl alcohol in DMSO under the sequential action of NH_4Br and KOH affords (*E*)-1-arylmethylidene-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazolines or (*E*)-1-arylmethylidene-1,2,3,3a-tetrahydro-5*H*-pyrrolo-[1,2-*a*][3,1]benzoxazines; the latter without substituents in the 3-position easily isomerize into the corresponding 2-arylmethyl-1-(2-hydroxymethylphenyl)pyrroles.

In last years, considerable attention is paid to syntheses of complex organic molecules with high efficiency and selectivity.[1] One of approaches implies a one-pot cascade cyclization of simple and available precursors leading to polycyclic structures. In particular, cyclizations of acetylenic carbonyl compounds with various binucleophiles giving fused N-heterocycles are intensively studied. Earlier,[2,3] we have proposed an original access to bicyclic *N*,*N*-ene aminals, namely, 6-arylmethylideneoctahydropyrrolo-[1,2-*a*]pyrimidines and 5-arylmethylidenehexahydropyrrolo-[1,2-*a*]imidazoles, by reaction of 1-(alk-1-ynyl)-1-chlorocyclo-propanes with lithiated aliphatic diamines. Further we have shown[5–7] that anionic cyclization of alk-4-ynals with aliphatic diamines, amino alcohols and amino thiols in the superbasic KOH–DMSO system[8] is more versatile and experimentally convenient method for synthesis of these compounds. Unlike other known cyclization means[9] of acetylenic carbonyl compounds with amines giving mostly endocyclic olefinic products, our approach is distinguished by unusual chemo- and stereoselectivity towards compounds with exocyclic double bond. Besides our works, only two communications[10,11] describing formation of 5-*exo*-*dig*-cyclized products in reactions of alk-4-ynals with 2-aminoethanol derivatives, have been published so far.

It seems of obvious interest to extend this chemistry on new types of substrates. In this work, alk-4-ynals were reacted with aromatic amines bearing additional nucleophilic center, namely, *o*-aminobenzylamine and *o*-aminobenzyl alcohol. The anticipated products should be fused tricyclic compounds of 1,2,3,4-tetra-hydroquinazoline and 1,4-dihydro-2*H*-[3,1]benzoxazine series incorporating enamine fragment with exocyclic double bond. These compounds would seem promising taking into account the literature data on biological activity of tetrahydroquinazoline[12–21] and benzoxazine[22–26] derivatives.

Our initial experiments showed that *o*-aminobenzyl alcohol reacted with alk-4-ynals noticeably slower than previously studied aliphatic diamines[5,6] and amino alcohols[7]. In fact, stirring of equi-molar amounts of aldehyde **1a** and amino alcohol **2** in DMSO for 3 h did not cause significant conversion of the reactants (Scheme 1). Literature data[27] indicate that such type of reactions should be promoted by weak acids including ammonium bromide,[28] which was successfully employed for the preparation of benzimidazoles from aromatic aldehydes and 1,2-diaminobenzene.

Really, addition of 0.25 equiv. of NH_4Br strongly accelerates the **1a** + **2** reaction in DMSO giving the sole benzoxazine product **3a** with ~65% conversion in 3 h while the full conversion was



Starting aldehyde	Reaction time with NH_4Br/h	Reaction time with KOH/h	Product	Yield (%)
1a	20	2	**4a**	64
1b	20	2	**4b**	73
1c	2	0.5	**5a**	70
1d	2	0.5	**4d**	76

Compound **4d** undergoes quantitative isomerization into pyrrole **5b** upon heating in $CDCl_3$ at 50 °C for 20 min.

Scheme 1

achieved in 20 h. Aldehyde **1b** reacts similarly, whereas for less sterically hindered alkynals **1c**,**d** the process is complete within 2 h. In all cases yields of benzoxazine derivatives **3a–d**, determined from NMR spectra, were nearly quantitative.

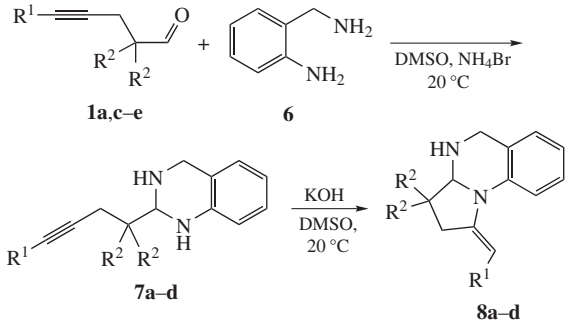
Addition of 4-fold molar excess of powdered KOH to the solutions of compounds **3a**,**b** in DMSO at room temperature results in fast intramolecular *exo*-*dig*-hydroamination of the triple bond leading to new fused 1-arylmethylidene-1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazines **4a**,**b** in 64–73% yields.†

† *1,2,3,3a-Tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazines* **4a**,**b**,**d** *and 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazolines* **8a–d** *(general procedure)*. A solution of alkynal **1** (1 mmol) in 3 ml of DMSO was slowly added with stirring to a solution of amine **2** or **6** (1 mmol) in 3 ml of anhydrous DMSO. Then NH_4Br (24 mg, 0.25 mmol) was added, and

Like previously studied[5,6] analogous cyclization of 2-(alk-3-ynyl)hexahydropyrimidines, this process is highly stereoselective providing exclusively *E*-isomers of products **4**. Their structure was confirmed by 2D NOESY spectra manifesting correlations between the *ortho*-protons of aryl substituent (R^1) and the 2-positioned methylene protons of the polycycle, as well as between olefinic proton and 9-positioned CH-fragment.

Cyclization of compounds **3c**,**d** having no α-branching in alkynyl fragment, according to the NMR spectra of reaction mixtures, also brings about *E*-isomers of corresponding 1-arylmethylidene-tetrahydro-5*H*-pyrrolo[1,2-*a*][3,1]benzoxazines **4c**,**d**. However, our attempts to isolate pure compound **4c** failed. After conventional aqueous workup, extraction and removal of the solvent under reduced pressure, *N*-(2-hydroxymethylphenyl)pyrrole **5a** was obtained in 70% yield. Obviously, it originated from ring opening in compound **4c**, which occurs even at room temperature. Benzoxazine **4d** bearing 4-trifluoromethylbenzylidene substituent is more stable and can be isolated from reaction mixture with purity exceeding 90%. However, heating it in $CDCl_3$ at 50 °C for 15 min causes its clean isomerization into pyrrole **5b**.

Similar processing of 5-arylalk-4-ynals **1a**,**c–e** with *o*-aminobenzylamine **6** affords the corresponding new (*E*)-1-arylmethylidene-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazolines **8a–d** in 65–74% yields (Scheme 2).† Unlike relative benzoxazines **4**, diaza analogues **8** are stable and easily isolable regardless of their substitution pattern. It is worth noting that base-catalyzed intramolecular hydroamination of triple bond in intermediates **7a–d** proceeds chemoselectively and exclusively with participation of anilinic amino group. This can be explained by higher acidity of aromatic amines compared to aliphatic ones and, therefore, enhanced ability to generate the corresponding anilide anion under the strong basic conditions. Importantly, our attempts to promote **3** → **4** or **7** → **8** cyclizations on using less basic anhydrous K_2CO_3 both at ~20 and at 85–90 °C were unsuccessful. Stirring of solutions of dihydrobenzoxazine **3a** or tetrahydroquinazoline **7a** with five-fold molar excess of K_2CO_3 in DMSO does not result in any reaction both at room temperature and at 85–90 °C.



1a, **7a**, **8a** R^1 = Ph, R^2 = Me
1c, **7b**, **8b** R^1 = 3,4-$F_2C_6H_3$, R^2 = H
1d, **7c**, **8c** R^1 = 4-$CF_3C_6H_4$, R^2 = H
1e, **7d**, **8d** R^1 = 3,4-$F_2C_6H_3$, R^2 = Me

Starting aldehyde	Reaction time with NH_4Br/h	Reaction time with KOH/h	Product	Yield (%)
1a	2	2	**8a**	68
1c	2	0.5	**8b**	65
1d	2	0.5	**8c**	74
1e	2	2	**8d**	65

Scheme 2

In summary, we have developed a new efficient one-pot chemo- and stereoselective synthesis of previously unknown (*E*)-1-arylmethylidene-1,2,3,3a-tetrahydro-5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazines and (*E*)-1-arylmethylidene-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinazolines from 5-arylalk-4-ynals by their sequential treatment with NH_4Br and KOH in DMSO. The products obtained seem multipurpose promising.

This work was supported by the Russian Foundation for Basic Research (grant no. 15-03-08195A).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.002.

References

1 V. P. Ananikov, E. A. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2015, **25**, 75.
2 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Mendeleev Commun.*, 2008, **18**, 300.
3 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Russ. Chem. Bull., Int. Ed.*, 2010, **59**, 1451 (*Izv. Akad. Nauk, Ser. Khim.*, 2010, 1418).
4 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Mendeleev Commun.*, 2013, **23**, 31.
5 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Mendeleev Commun.*, 2013, **23**, 140.
6 V. D. Gvozdev, K. N. Shavrin and O. M. Nefedov, *Russ. Chem. Bull., Int. Ed.*, 2013, **62**, 2430 (*Izv. Akad. Nauk, Ser. Khim.*, 2013, 2430).
7 V. D. Gvozdev, K. N. Shavrin and O. M. Nefedov, *Russ. Chem. Bull., Int. Ed.*, 2014, **63**, 409 (*Izv. Akad. Nauk, Ser. Khim.*, 2014, 409).
8 B. A. Trofimov and E. Yu. Schmidt, *Russ. Chem. Rev.*, 2014, **83**, 600.
9 (*a*) N. T. Patil, A. K. Mutyala, A. Konala and R. B. Tella, *Chem. Commun.*, 2012, **48**, 3094; (*b*) V. Rustagi, T. Aggarwal and A. K. Verma, *Green Chem.*, 2011, **13**, 1640; (*c*) Y. Tokimizu, Y. Ohta, H. Chiba, S. Oishi, No. Fujii and H. Ohno, *Tetrahedron*, 2011, **67**, 5168; (*d*) T. K. Chaitanya, K. S. Prakash and R. Nagarajan, *Tetrahedron*, 2011, **67**, 6934; (*e*) H. Gao and J. Zhang, *Adv. Synth. Catal.*, 2009, **351**, 85; (*f*) M. Yu, Y. Wang, C.-J. Li and X. Yao, *Tetrahedron Lett.*, 2009, **50**, 6791; (*g*) H. Zhou, H. Jin, S. Ye, X. He and J. Wu, *Tetrahedron Lett.*, 2009, **50**, 4616; (*h*) Y. Ye, Q. Ding and J. Wu, *Tetrahedron*, 2008, **64**, 1378; (*i*) H.-C. Ouyang, R.-Y. Tang, P. Zhong, X.-G. Zhang and J.-H. Li, *J. Org. Chem.*, 2011, **76**, 223;

---

the resulting mixture was stirred at room temperature for time indicated in Schemes 1 and 2. Thereafter, freshly powdered KOH (280 mg, 5 mmol) was added, and the resulting suspension was stirred for 0.5–2 h (for exact time, see Schemes 1 and 2). Then, 30 ml of water and 30 ml of Et_2O were added, and the organic layer was separated. The aqueous layer was additionally extracted with Et_2O (3×10 ml). The combined organic layers were washed three times with water, dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was subjected to recrystallization from light petroleum to afford products **4a**,**b** and **8a–d** or to flash chromatography to give compounds **4d** and **5a**.

*(1*E*)-1-Benzylidene-3,3-dimethyl-1,2,3,3a-tetrahydro-5*H*-pyrrolo-[1,2-*a*][3,1]benzoxazine* **4a** was prepared from aldehyde **1a** and amine **2** and isolated in 64% yield, mp 78–79 °C. ^{1}H NMR, δ: 1.21 (s, 3H, Me), 1.31 (s, 3H, Me), 2.82 (dd, 1H, =CC*H*H, ^2J 15.0 Hz, ^4J 2.0 Hz), 2.85 (dd, 1H, =CC*H*H, ^2J 15.0 Hz, ^4J 1.7 Hz), 4.65 (s, 1H, NCHO), 5.04 (s, 2H, OCH_2), 6.30 (br.s, 1H, PhC*H*=), 7.0–7.4 (m, 8H, Ar), 7.61 (d, 1H, Ar, ^3J 8.2 Hz). ^{13}C NMR, δ: 21.7 (Me), 27.1 (Me), 38.7 (C^3), 43.6 (C^2), 67.6 (C^5), 95.3 (C^{3a}), 99.1 (PhCH=), 120.5, 122.0, 124.9, 126.8 (C^6, C^7, C^8, C^9), 124.1, 127.3, 128.2 (Ph), 125.2 (C^{5a}), 138.9, 139.1, 143.8 (C^{9a}, C^1; C^1, Ph). HRMS, *m*/*z*: 290.1543, 291.1613, 292.1684 (calc. for $C_{20}H_{21}NO$, *m*/*z*: 290.1539 $[M-H]^+$, 291.1618 $[M]^+$, 292.1696 $[M+H]^+$).

*(1*E*)-1-Benzylidene-3,3-dimethyl-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-*a*]quinazoline* **8a** was prepared from aldehyde **1a** and amine **6** and isolated in 68% yield, mp 118–119 °C. ^{1}H NMR, δ: 1.01 (s, 3H, Me), 1.29 (s, 3H, Me), 1.95 (br.s, 1H, NH), 2.71 (dd, 1H, =CC*H*H, ^2J 14.0 Hz, ^4J 2.1 Hz), 2.77 (br.d, 1H, =CC*H*H, ^2J 14.0 Hz), 4.15 (d, 1H, NHC*H*H, ^2J 17.1 Hz), 4.23 (d, 1H, NHC*H*H, ^2J 17.1 Hz), 4.33 (s, 1H, NCHN), 6.33 (br.s, 1H, PhC*H*=), 6.87 (t, 1H, Ar, *J* 7.4 Hz), 7.0–7.4 (m, 7H, Ar), 7.73 (d, 1H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 20.8 (Me), 26.0 (Me), 38.2 (C^3), 44.3, 47.5 (C^2, C^5), 80.8 (C^{3a}), 100.6 (PhCH=), 116.8, 199.9, 126.3, 127.0 (C^6, C^7, C^8, C^9), 123.9, 127.3, 128.2 (Ph), 124.0 (C^{5a}), 139.6, 140.0, 141.5 (C^{9a}, C^1; C^1, Ph). HRMS, *m*/*z*: 289.1704, 290.1767, 291.1857 (calc. for $C_{20}H_{22}N_2$, *m*/*z*: 289.1699 $[M-H]^+$, 290.1778 $[M]^+$, 291.1856 $[M+H]^+$).

For characteristics of compounds **4b**,**d**, **5a**,**b** and **8b–d**, see Online Supplementary Materials.

(*j*) Yu. Ohta, Yu. Kubota, T. Watabe, H. Chiba, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem*., 2009, **74**, 6299; (*k*) J. Chen, B. Liu, Y. Chen, Q. He and C. Yang, *RSC Adv.*, 2014, **4**, 11168; (*l*) X. Wang, G. Qiu, L. Zhang and J. Wu, *Tetrahedron Lett.*, 2014, **55**, 962; (*m*) R. R. Jha, A. K. Danodia, S. Kumar and A. K. Verma, *Tetrahedron Lett*., 2014, **55**, 610; (*n*) R. R. Jha, R. K. Saunthwal and A. K. Verma, *Org. Biomol. Chem*., 2014, **12**, 552; (*o*) S. U. Dighe and S. Batra, *Tetrahedron*, 2013, **69**, 9875; (*p*) N. T. Patil, A. Konala, S. Sravanti, A. Singh, R. Ummanni and B. Sridhar, *Chem. Commun*., 2013, **49**, 10109.

10 O. David, S. Calvet, F. Chau, C. Vanucci-Bacqué, M.-C. Fargeau-Bellassoued and G. Lhommet, *J. Org. Chem.*, 2004, **69**, 2888.

11 R. R. Jha, T. Aggarwal and A. K. Verma, *Tetrahedron Lett*., 2014, **55**, 2603.

12 Z. Chen, G. Hu, D. Li, J. Chen, Y. Li, H. Zhou and Y. Xie, *Bioorg. Med. Chem*., 2009, **17**, 2351.

13 G. Dong, S. Wang, Z. Miao, J. Yao, Y. Zhang, Z. Guo, W. Zhang and C. Sheng, *J. Med. Chem.*, 2012, **55**, 7593.

14 F. H. Darras, B. Kling, J. Heilmann and M. Decker, *ACS Med. Chem. Lett.*, 2012, **3**, 914.

15 R. A. Johnson, R. R. Gorman, R. J. Wnuk, N. J. Crittenden and J. W. Aiken, *J. Med. Chem.*, 1993, **36**, 3202.

16 E. Perola, K. Xu, T. M. Kollmeyer, S. H. Kaufmann, F. G. Prendergast and Y.-P. Pang, *J. Med. Chem.*, 2000, **43**, 401.

17 S. M. Sondhi, R. N. Goyal, A. M. Lahoti, N. Singh, R. Shukla and R. Raghubir, *Bioorg. Med. Chem.*, 2005, **13**, 3185.

18 C. Marchand, J. A. Beutler, A. Wamiru, S. Budihas, U. Moellmann, L. Heinisch, J. W. Mellors, S. F. Le Grice and Y. Pommier, *Antimicrob. Agents Chemother*., 2008, **52**, 361.

19 B. Insuasty, H. Torres, J. Quiroga, R. Abonia, M. Nogueras, A. Sanchez, M. Sortino, S. Zacchino and J. Low, *Heterocycl. Commun*., 2003, **9**, 153.

20 I. P. Jakopovic, G. Kragol, A. K. Forrest, C. S. V. Frydrych, V. Timac, S. Kapic, M. M. Kugor, M. Ilija, H. I. Paljetak, D. Jelic, D. J. Holmes, D. M. B. Hickey, D. Verbanac, V. Erakovichaber and S. Alihodic, *Bioorg. Med. Chem*., 2010, **18**, 6578.

21 Y. Hitotsuyanagi, Y. Naka, K. Yamagami, A. Fujii and T. Tahara, *J. Chem. Soc., Chem. Commun*., 1995, 49.

22 (*a*) J. B. Chylinska, M. Janowiec and T. B. Urbarnsky, *J. Pharmacol*., 1971, **43**, 649; (*b*) G. P. Moloney, D. J. Craik and M. N. Iskander, *J. Pharm. Sci*., 1992, **81**, 692; (*c*) N. A. Shakil, A. Dhawan, N. K. Sharma, V. Kumar, S. Kumar, M. Bose, H. G. Raj, C. E. Olsen, A. L. Cholli, L. A. Samuelson, J. Kumar, A. C. Watterson, V. S. Parmar and A. K. Prasad, *Indian J. Chem., Sect. B*, 2003, **42**, 1958; (*d*) B. M. Gurupadayya, Y. N. Manohara and M. Gopal, *Indian J. Heterocycl. Chem.*, 2005, **15**, 113.

23 S. Gemma, C. Camodeca, M. Brindisi, S. Brogi, G. Kukreja, S. Kunjir, E. Gabellieri, L. Lucantoni, A. Habluetzel, D. Taramelli, N. Basilico, R. Gualdani, F. Tadini-Buoninsegni, G. Bartolommei, M. R. Moncelli, R. E. Martin, R. L. Summers, S. Lamponi, L. Savini, I. Fiorini, M. Valoti, E. Novellino, G. Campiani and S. Butini, *J. Med. Chem*., 2012, **55**, 10387.

24 M. Largeron, B. Lackhart, B. Pfeiffer and M. B. Fleury, *J. Med. Chem.*, 1999, **42**, 5043.

25 E. N. Koini, P. Papazafiri, A. Vassilopoulos, M. Koufaki, Z. Horváth, I. Koncz, L. Virág, G. J. Papp, A. Varró and T. Calogeropoulou, *J. Med. Chem*., 2009, **52**, 2328.

26 H. Wang and A. Ganesan, *J. Org. Chem*., 2000, **65**, 1022.

27 (*a*) I. B. Masesane, E. Muriithi and T. H. Tabane, *Bull. Chem. Soc. Ethiop*., 2014, **28**, 301; (*b*) J. Mulzer, O. Langer, M. Hiersemann, J. W. Bats, J. Buschmann and P. Luger, *J. Org. Chem.*, 2000, **65**, 6540; (*c*) A. Ignacio, J. Alcazar, J. M. Alonso, A. Diaz, J. Fernandez, P. Gil, L. Iturrino, E. Matesanz, T. F. Meert, A. Megens and V. K. Sipido, *Bioorg. Med. Chem. Lett*., 2002, **12**, 249.

28 B. C. Raju, N. D. Theja and J. A. Kumar, *Synth. Commun.*, 2009, **39**, 175.

Received: 15th April 2015; Com. 15/4602