Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2016, **26**, 3–5
Mendeleev Communications

Stereoselective one-pot synthesis of (1*Z*)- and (1*E*)-1-arylmethylidene-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles by cyclization of alk-4-ynals with *o*-diaminobenzene

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.2016.01.002

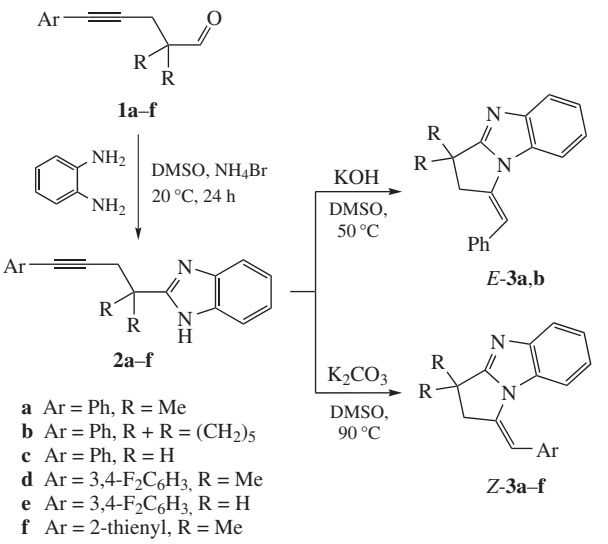
Cyclization of alk-4-ynals with *o*-diaminobenzene in DMSO under the sequential action of NH_4Br and base (KOH or K_2CO_3) affords 1-arylmethylidene-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles, which are formed selectively as *E*- or *Z*-isomers depending on the base used.

Pyrrolobenzimidazoles can be regarded as privileged scaffolds in pharmaceutical research.[1–4] The commonly used routes for their synthesis include rhodium-catalyzed cyclizations of *N*-alkenylbenzimidazoles,[5,6] cyclocondensation of pyrrolidones with *o*-bromoanilines,[7] annulation of benzimidazoles *via* intramolecular nucleophilic substitution[8] and cyclopropylimine rearrangement of 2-cyclopropylbenzimidazolium salts.[9] Other approaches to 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles by radical cyclization of alkylbenzimidazoles[10] and iodocyclization of 2-alkynylbenzimidazoles[11] have been reported.

Earlier we have proposed[12,13] an original method for the preparation of 6-(arylmethylidene)octahydropyrrolo[1,2-*a*]pyrimidines and 5-(arylmethylidene)hexahydropyrrolo[1,2-*a*]imidazoles based on the interaction of alk-4-ynals with aliphatic diamines in the KOH–DMSO medium. Then, this approach was extended[14] onto amino alcohols and amino thiols giving the corresponding fused oxazoles, oxazines and thiazoles with exocyclic double bond. Recently we have shown that the use of *o*-aminobenzylamine and *o*-aminobenzyl alcohol as a binucleophilic agent in reactions with alk-4-ynals in NH_4Br–KOH–DMSO system led to 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.[15]

Taking into account these results, we proposed that involvement of *o*-diaminoarenes into such a process would allow us to access 1-methylidenepyrrolobenzimidazole by the reaction sequence including oxidative cyclization into the corresponding benzimidazoles and intramolecular hydroamination of the triple bond by the action of benzimidazolic NH group. At present, only few examples of such compounds bearing iodo-, phenyl- and phenylethynyl substituents in methylidene fragment, have been described,[11] in all cases they were obtained as less sterically hindered *E*-isomers.

As a catalyst of the first step, condensation of alk-4-ynals with *o*-diaminobenzene, NH_4Br was chosen, since it had been successfully employed[16] in analogous reactions with aromatic aldehydes. Stirring of equimolar amounts of aldehydes **1a–f** and *o*-diaminobenzene in dry DMSO in the presence of NH_4Br at room temperature for 24 h, according to NMR spectra leads to the selective formation of corresponding 2-substituted benzimidazoles **2a–f** (Scheme 1). Note that despite of reported data,[16] where four-fold excess of NH_4Br was used, we found that 20 mol% of this salt was enough for our purpose. In separate experiments, benzimidazoles **2a**,**b** were isolated in individual state in 68 and 74% yields, respectively.



a Ar = Ph, R = Me
b Ar = Ph, R + R = $(CH_2)_5$
c Ar = Ph, R = H
d Ar = 3,4-$F_2C_6H_3$, R = Me
e Ar = 3,4-$F_2C_6H_3$, R = H
f Ar = 2-thienyl, R = Me

1, **2**	Base	*T*/°C	Time of reaction with base/h	Product	Yield (%)
a	KOH	50	48	*E*-**3a**	56
b	KOH	50	24	*E*-**3b**	48
c	KOH	50	24	–	–
a	K_2CO_3	90	72	*Z*-**3a**	75
b	K_2CO_3	90	24	*Z*-**3b**	52
c	K_2CO_3	90	240	*Z*-**3c**	37
d	K_2CO_3	90	24	*Z*-**3d**	57
e	K_2CO_3	90	12	*Z*-**3e**	32
f	K_2CO_3	90	12	*Z*-**3f**	78

Scheme 1

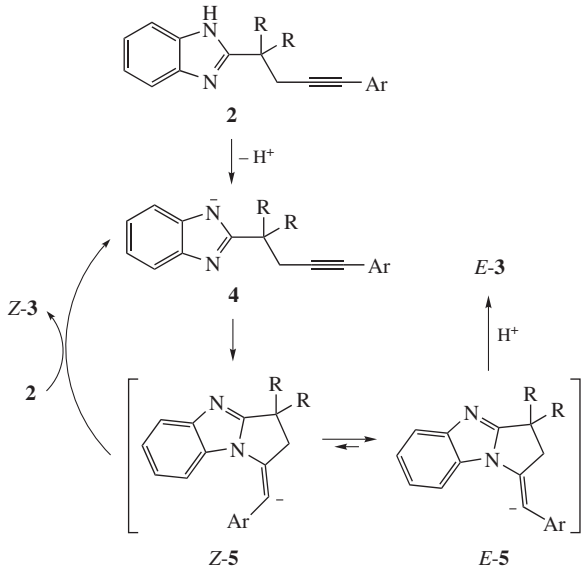
The sequential addition of 1.5-fold excess of freshly powdered KOH to the solutions of benzimidazoles **2a** or **2b** in DMSO with stirring at 50 °C for 48 h (for **2a**) or 24 h (for **2b**) caused their full conversion giving (*E*)-1-arylmethylidenepyrrolobenzimidazoles **3a**,**b** in 48–56% isolated yield based on starting aldehydes **1a**,**b**.

Similar attempted use of alk-4-ynals with α-protons to the carbonyl group was unsuccessful. Thus, addition of KOH to the solution of benzimidazole **2c**, which had been obtained by the interaction of aldehyde **1c** with *o*-diaminobenzene, yielded only polymeric products. Probably, the side processes involving relatively acidic hydrogen atoms at α-position to the benzimidazole fragment proceed significantly faster than the intramolecular hydroamination of the triple bond. In the meantime, the

replacement of KOH with less basic K_2CO_3 and increase in the reaction temperature to 90 °C allowed us to synthesize the target pyrrolobenzimidazoles **3a–f** from aldehydes **1a–f** regardless of their substitution pattern in reasonable yields (see Scheme 1).† Note that in this case the stereoselectivity of final product formation changes dramatically, and instead of *E*-isomers of compounds **3** more sterically hindered *Z*-isomers were formed in all cases. As it can be seen from the data obtained, replacement of phenyl group with more electron-withdrawing 2-thienyl or 3,4-difluorophenyl one, as well as introducing two alkyl groups into α-position of the starting aldehyde sufficiently facilitate intramolecular cyclization of benzimidazoles **2**, which, most likely, is due to increase in polarization of the triple bond.

Most likely, such significant difference in stereoselectivity depending on the base used can be explained as follows. In case of strongly basic KOH, benzimidazoles **2** undergo fast and complete deprotonation giving anions **4**, which was confirmed by the characteristic upfield shifts of signals of aromatic protons in benzimidazole system. Then the latter give vinylic anions *Z*-**5** as a result of 5-*exo*-*dig*-cyclization. Such stereoselectivity is in accordance with known data on intramolecular hydroamination of alkynes under the action of imidazoles[17] and indoles[18] under basic conditions. Due to high basicity of KOH–DMSO medium, these anions have enough time to isomerize into more thermodynamically stable *E*-**5** (such isomerization of vinylic anions derived from intramolecular addition of N-centered anions to the triple bond of alkynes in basic medium has been postulated, see ref. 19), which then trap proton from the reaction medium, forming *E*-isomers of 1-arylmethylidenepyrrolobenzimidazoles **3**.

If less basic K_2CO_3 is used, benzimidazoles **2** are deprotonated only to a little extent, and once intermediates *Z*-**5** are formed, they are protonated immediately by the action of starting compound



Scheme 2

2, generating anions **4**, which participate in the next reaction cycle, and *Z*-isomers of products **3** (Scheme 2).

Identification of *E*- and *Z*-isomers of benzimidazoles **3** was performed based on the 2D NOESY proton spectra. In case of *E*-isomers of **3a** and **3b** this spectrum shows correlations between methine proton at double bond and the proton at the 8-position, as well as between methylene fragment at the 2-position and *o*-protons in phenyl group. NOESY spectra of *Z*-isomers of compounds **3** exhibit characteristic correlations between olefinic proton and CH_2 fragment at the 2-position, and also between *o*-protons in aromatic group and the proton at the 8-position.

In summary, we have developed a new one-pot transition metal-free synthesis of 1-arylmethylidene-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]benzimidazoles from alk-4-ynals in DMSO–NH_4Br–base system. Important feature of this method is the possibility of controlling the stereoselectivilty of five-membered ring closure, which provides exclusive formation of *E*- or *Z*-isomers of target products depending on the base used.

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

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.01.002.

References

1 A. J. Charlson and J. S. Harrington, *Carbohydr. Res.*, 1975, **43**, 383.
2 D. H. H. Tsao, A. G. Sutherland, L. D. Jennings, Y. Li, T. S. Rush, J. C. Alvarez, W. Ding, E. G. Dushin, R. G. Dushin, S. A. Haney, C. H. Kenny, A. K. Malakian, R. Nilakantan and L. Mosyak, *Bioorg. Med. Chem.*, 2006, **14**, 7953.
3 H. Uchida, A. Asagarasu and T. Matsui, *US Patent Application 2013/0079306 A1*.
4 E. B. Skibo, *US Patent 6,998,413*, 2006 (*Chem. Abstr.*, 2006, **133**, 12985).
5 K. L. Tan, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2001, **123**, 2685.
6 A. S. Tsai, R. M. Wilson, H. Harada, R. G. Bergman and J. A. Ellman, *Chem. Commun.*, 2009, 3910.
7 K. Liubchak, K. Nazarenko and A. Tolmachev, *Tetrahedron*, 2012, **68**, 2993.
8 G. Bastug, C. Eviolitte and I. E. Marko, *Org. Lett.*, 2012, **14**, 3502.
9 Y. V. Tomilov, D. N. Platonov, A. E. Frumkin, D. L. Lipilin and R. F. Salikov, *Tetrahedron Lett.*, 2010, **51**, 5120.
10 S. M. Allin, W. R. Bowman, R. Karima and S. S. Rahman, *Tetrahedron Lett.*, 2006, **62**, 4306.

† *1-Arylmethylidene-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazoles* **3a–f** *(general procedure)*. A solution of *o*-diaminobenzene (216 mg, 2 mmol) in 3 ml of anhydrous DMSO was slowly added to a solution of aldehyde **1** (2 mmol) in 3 ml of DMSO. Then, NH_4Br (39 mg, 0.4 mmol) was added, and the resulting mixture was stirred at room temperature for 24 h in the presence of dry air. Thereafter freshly powdered KOH (180 mg, 3 mmol in case of *E*-**3a** and *E*-**3b**) or anhydrous K_2CO_3 (830 mg, 6 mmol, in case of *Z*-**3a–f**) was added, and the resulting suspension was stirred in argon atmosphere for time and at temperature specified in Scheme 1 (NMR monitoring). 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 extracts were washed thrice with water, dried (Na_2SO_4), and concentrated. Column chromatography of the residue on silica gel [hexane–Et_2O (20:1 → 5:1) as eluent] gave compounds *E*-**3a**,**b** or *Z*-**3a–f**.

*(1*E*)-1-Benzylidene-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole E*-**3a** was prepared from aldehyde **1a** in 56% yield, mp 135–137 °C. ^{1}H NMR, δ: 1.46 (s, 6H, 2Me), 3.27 (d, 2H, CH_2, ^4J 2.2 Hz), 6.69 (t, 1H, PhC*H*=, ^4J 2.2 Hz), 7.10–7.36 (m, 7H, Ph, C^7H, C^8H), 7.63–7.72 (m, 2H, C^5H, C^6H). ^{13}C NMR, δ: 27.4 (2Me), 36.4 (C^3), 47.9 (C^2), 108.9 (Ph*C*H=), 111.4, 120.1, 122.9, 123.2 (C^5, C^6, C^7, C^8), 126.5, 127.9, 128.7 (Ph), 129.93, 149.0 (C^{4a}, C^{8a}), 135.5, 136.0 (C^1, Ph; C^1), 167.0 (C^{3a}). HRMS, *m/z*: 275.1545 (calc. for $C_{19}H_{18}N_2$, $[M+H]^+$, *m/z*: 275.1543).

*(1*Z*)-1-Benzylidene-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole Z*-**3a** was prepared from aldehyde **1a** in 75% yield, mp 121–122 °C. ^{1}H NMR, δ: 1.57 (s, 6H, 2Me), 3.13 (d, 2H, CH_2, ^4J 1.5 Hz), 5.76 (d, 1H, benzimidazole, ^3J 8.2 Hz), 6.18 (br. s, 1H, PhC*H*=), 6.77–6.89 (m, 1H, benzimidazole), 7.08–7.19 (m, 1H, benzimidazole), 7.13–7.25 (m, 2H, Ph), 7.26–7.41 (m, 3H, Ph), 7.67 (d, 1H, benzimidazole, ^3J 8.1 Hz). ^{13}C NMR, δ: 26.4 (2Me), 36.5 (C^3), 51.6 (C^2), 108.4 (Ph*C*H=), 114.4, 119.4, 122.0, 122.5 (C^5, C^6, C^7, C^8), 127.2, 128.2, 129.6 (Ph), 130.3, 148.0 (C^{4a}, C^{8a}), 133.7, 135.9 (C^1, Ph; C^1), 168.8 (C^{3a}). HRMS, *m/z*: 275.1538 (calc. for $C_{19}H_{18}N_2$, $[M+H]^+$, *m/z*: 275.1543).

For characteristics of compounds **2a**,**b**, *E*-**3b** and *Z*-**3b–f**, see Online Supplementary Materials.

11 X. Zhang, Y. Zhou, H. Wang, D. Guo, D. Ye, Y. Xu, H. Jiang and H. Liu, *Adv. Synth. Catal*., 2011, **353**, 1429.
12 K. N. Shavrin, V. D. Gvozdev and O. M. Nefedov, *Mendeleev Commun.*, 2013, **23**, 140.
13 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).
14 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).
15 V. D. Gvozdev, K. N. Shavrin, M. P. Egorov and O. M. Nefedov, *Mendeleev Commun.*, 2015, **25**, 329.
16 B. C. Raju, N. D. Theja and J. A. Kumar, *Synth. Commun*., 2009, **39**, 175.
17 M. Patel, R. K. Saunthawal and A. K. Verma, *Tetrahedron Lett*., 2014, **55**, 1310.
18 A. K. Verma, M. Patel, M. Joshi, P. R. Likhar, R. K. Tiwari and K. Parang, *J. Org. Chem.*, 2014, **79**, 172.
19 C. Kanazawa and M. Terada, *Chem. Asian J*., 2009, **4**, 1668.

Received: 22nd July 2015; Com. 15/4691