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Selective one-pot synthesis of 11-arylmethylidene-11*H*-isoindolo-[2,1-*a*]benzimidazoles and 6-arylbenzimidazo[2,1-*a*]isoquinolines from *o*-alkynylbenzaldehydes and *o*-diaminobenzenes

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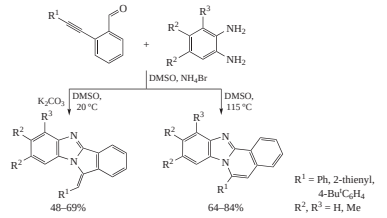
Cyclization of *o*-alkynylbenzaldehydes with *o*-diaminobenzenes in DMSO under the sequential action of NH_4Br and K_2CO_3 affords 11-arylmethylidene-11*H*-isoindolo[2,1-*a*]-benzimidazoles as a result of 5-*exo*-*dig* ring closure; whereas replacement of treating with K_2CO_3 by heating at 110–115 °C results in 6-*endo*-*dig* cyclization with formation of 6-aryl-benzimidazo[2,1-*a*]isoquinolines.



Fused N-heterocyclic building blocks are ubiquitous in natural products and play a significant role in the pharmaceutical and agrochemical industries.[1] Among numerous known fused heterocyclic systems, benzimidazoisoquinolines attract special attention as they show important biological properties, *e.g.* anti-HIV-1, anticancer, antimicrobial, and antifungal activities.[2] Methods for their synthesis are based mainly on the reactions of 2-alkynylbenzaldehydes with *o*-phenylenediamines, which require harsh conditions.[3,4] Also, efficient copper-catalyzed syntheses of benzimidazoisoquinolines *via* reactions of 2-alkynylbenzaldehydes and benzenediamines in the presence of NBS or iodine[5] as well as under Ag^I catalysis in water[6] were described. Recently, cascade synthesis of alkyl 6-aminobenzimidazo[2,1-*a*]isoquinoline-5-carboxylates based on the reaction between 2-(*o*-bromoaryl)-benzimidazoles and cyanoacetic acid derivatives, has been developed.[7]

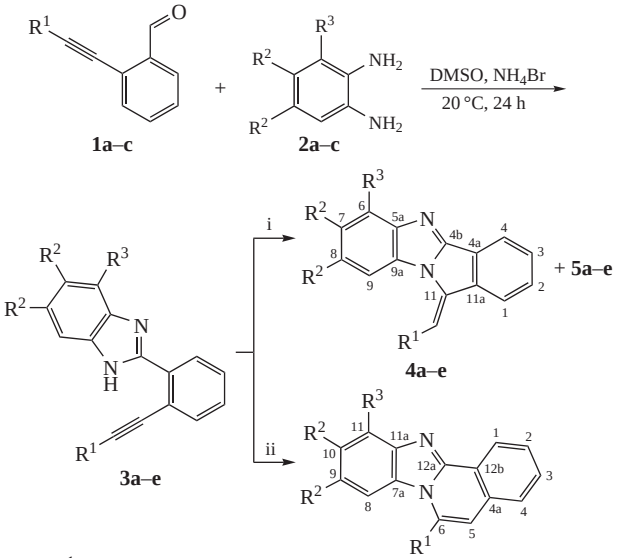
11-Methylidene-11*H*-isoindolo[2,1-*a*]benzimidazoles, which are isomers of benzimidazoisoquinolines, are less investigated. A limited number of these compounds have been synthesized[8] by cyclization of 2-arylbenzimidazoles with carboxylic acids in the presence of $Pd(OAc)_2$. However, they can serve as potential scaffolds due to the presence of pharmacophore isoindole[9] and benzimidazole[10] fragments.

Earlier we have developed a universal strategy for synthesis of various N,N-[11–13] and N,O-heterocyclic[13,14] systems based on the interaction of alk-4-ynals with corresponding diamines or amino alcohols in DMSO under the action of bases. Further it was found,[15,16] that the use of *o*-diaminoarenes as binucleophilic agents in reactions with alk-4-ynals in NH_4Br–base–DMSO system is an efficient, transition metal-free and stereoselective procedure to access 1-arylmethylidene-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]benzimidazoles.

Taking into account these results, we supposed that involvement of *o*-alkynylbenzaldehydes into similar transformations would allow one to obtain 11-arylmethylidene-11*H*-isoindolo-[2,1-*a*]benzimidazoles or 6-arylbenzimidazo[2,1-*a*]isoquinolines as a result of reaction sequence including oxidative cyclization into the corresponding benzimidazoles and intramolecular hydroamination of the triple bond in 5-*exo*-*dig* or 6-*endo*-*dig* fashion.

Similar to analogous reaction of alk-4-ynals, stirring equimolar amounts of aldehydes **1a**–**c** and *o*-diaminobenzenes **2a**–**c** in dry DMSO in the presence of NH_4Br for 24 h at room temperature, according to NMR spectra, selectively gives the corresponding 2-substituted benzimidazoles **3a**–**e** (Scheme 1). In separate experiments, benzimidazoles **3b** and **3c** were individually isolated in 67 and 78% yields, respectively.

Attempt to perform selective intramolecular cyclization of these compounds under the action of KOH, which had been successfully employed in analogous processes with 2-(alk-4-ynyl)benzimidazoles,[16] failed. Thus, stirring the solution of



1a R^1 = Ph
1b R^1 = 2-thienyl
1c R^1 = 4-Bu^{t}C$_6$H$_4$

2a R^2 = R^3 = H
2b R^2 = Me, R^3 = H
2c R^2 = H, R^3 = Me

3–**5**: **a** R^1 = Ph, R^2 = R^3 = H
b R^1 = Ph, R^2 = Me, R^3 = H
c R^1 = 2-thienyl, R^2 = R^3 = H
d R^1 = 2-thienyl, R^2 = H, R^3 = Me
e R^1 = 4-Bu^{t}C$_6$H$_4$, R^2 = R^3 = H

Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMSO, 20 °C; ii, DMSO, 110–115 °C.

Table 1 Synthesis of products **4a**–**e** and **5a**–**e**.

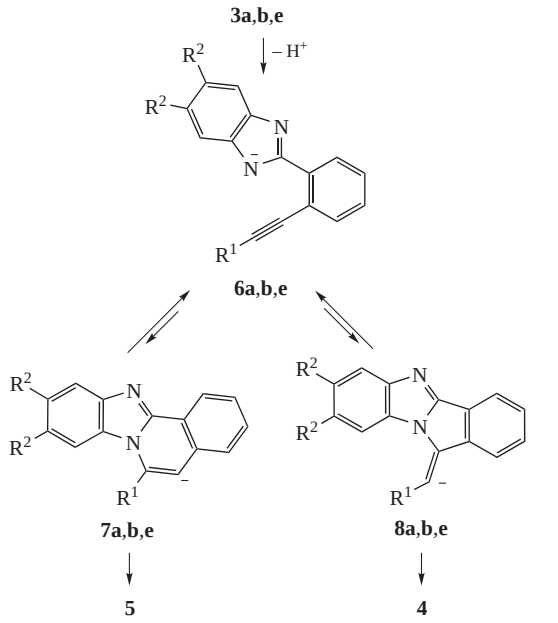
Reactants	Reaction conditions[a]	Reaction time / h	Product ratio by NMR [isolated yield (%)]
1a + **2a**	i	3	**4a** (59) : **5a**, 5 : 1
	ii	4	**5a** (80)
1a + **2b**	i	4	**4b** (52) : **5b**, 5.5 : 1
	ii	4	**5b** (84)
1b + **2a**	i	2	**4c** (69) : **5c**, 13 : 1
	ii	4	**5c** (78)
1b + **2c**	i	2	**4d** (65) : **5d**, 10 : 1
	ii	4	**5d** (65)
1c + **2a**	i	10	**4e** (48) : **5e**, 2.9 : 1
	ii	5	**5e** (72)

[a] See Scheme 1.

benzimidazole **3a** in DMSO with twofold molar excess of powdered KOH at room temperature, according to the NMR spectroscopic data, caused full conversion of the starting material with formation of a complex mixture where overall content of products **4a** and **5a** (1.7 : 1 ratio) did not exceed 50%. Luckily, replacement of KOH by less basic K_2CO_3 provided better results. Stirring the solution of benzimidazole **3a** with twofold excess of this reagent for 3 h resulted in more selective and efficient intramolecular cyclization affording isoindolo[2,1-*a*]benzimidazole **4a** and 6-arylbenzimidazo[2,1-*a*]isoquinoline **5a** in 5 : 1 ratio and overall yield of ~90%. Similar results were obtained in cyclization of benzimidazole **3b**, whereas benzimidazoles **3c**,**d** bearing more electronegative thienyl group at the triple bond underwent the ring closure more regioselectively giving the corresponding products **4c**, **5c** and **4d**, **5d** in 13 : 1 and 10 : 1 ratios, respectively. On the contrary, reaction of benzimidazole **3e** with K_2CO_3 appears to be less regioselective, and products **4e** and **5e** were formed in 2.9 : 1 ratio (NMR). This can be explained by reduced electronegativity of 4-*tert*-butylphenyl group compared to the phenyl and thienyl ones, which discourages anionic 5-*exo*-*dig*-hydroamination of the triple bond. After common aqueous workup of reaction mixture, individual compounds **4a**–**e** can be isolated by column chromatography (for **4a**, **4c**–**e**) or double recrystallization from hexane (for **4b**) in 48–69% yields.†

Experimental data are in good agreement with B3LYP/6+31G(d,p) calculations of intramolecular cyclization of N-anions **6a**,**b**,**e**, which is a probable key step of the studied transformation. These calculations showed that 6-*endo*-*dig*-cyclization into six-membered anions **7** (ΔE_0 = 6.2–6.7 kcal mol^{-1}) is thermodynamically more favorable than 5-*exo*-*dig*-cyclization into anions **8** (ΔE_0 = 10.1–12.0 kcal mol^{-1}). However, the latter process is characterized by lower activation barrier (18.2–19.2 kcal mol^{-1}), which makes it dominant reaction route (Scheme 2).

Note that the formation of isoindolobenzimidazoles **4** from aldehydes **1** proceeds stereoselectively, giving exclusively products with *Z*-configured exocyclic double bond. Their identification was performed based on the 2D NOESY proton spectra, showing correlations between methine proton at the double bond and the proton at the 1-position, as well as between *ortho*-protons in arylmethylidene substituent and the proton at the 9-position. Also, in case of compound **4d**, only one regioisomer bearing methyl group at the 6-position was formed, which points to high sensitivity of base-induced ring closure in benzimidazoles **3** to steric environment of nitrogen atoms.



	R^1	R^2	E_a / kcal mol^{-1}		ΔE_0 / kcal mol^{-1}	
			6 → 7	**6 → 8**	**7**	**8**
a	Ph	H	22.3	18.9	6.7	11.2
b	Ph	Me	21.7	18.2	6.2	10.1
e	4-Bu^{t}C$_6$H$_4$	H	22.0	19.2	6.5	12.0

Scheme 2

We have also found that minor products of the above reaction, benzimidazo[2,1-*a*]isoquinolines **5a**–**e**, can be selectively obtained in 64–84% yields by simple heating solutions of benzimidazoles **3a**–**e** in DMSO at 110–115 °C for 4–5 h (Scheme 1).‡

† *11-Arylmethylidene-11*H-*isoindolo[2,1-*a*]benzimidazoles* **4a**–**e** *(general procedure)*. A solution of *o*-diaminobenzene **2** (1 mmol) in anhydrous DMSO (2 ml) was slowly added to a solution of the corresponding aldehyde **1** (1 mmol) in DMSO (2 ml). Then, NH_4Br (39 mg, 0.4 mmol) was added and the resulting mixture was stirred in the contact with dry air at room temperature for 24 h. Thereafter, freshly powdered anhydrous K_2CO_3 (275 mg, 2 mmol) was added, and the resulting suspension was stirred in argon atmosphere at room temperature for time specified in Table 1 (the reaction progress was monitored by NMR). Then, water (30 ml) and Et_2O (30 ml) 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 column chromatography on silica gel or to double recrystallization from hexane–THF to give compounds **4a**–**e**.

*(11Z)-11-Benzylidene-11*H-*isoindolo[2,1-*a*]benzimidazole* **4a** was prepared from aldehyde **1a** and diamine **2a** and isolated in 59% yield by column chromatography [hexane–THF (3 : 1) as eluent]. ^{1}H NMR, δ: 5.79 (d, 1H, C^{9}H, ^3J 8.2 Hz), 6.87 (dd, 1H, C^{8}H, ^3J 8.2 Hz, ^3J 7.5 Hz), 7.13 (s, 1H, C*H*Ph), 7.17 (dd, 1H, C^{7}H, ^3J 8.0 Hz, ^3J 7.5 Hz), 7.44–7.59 (m, 7H, C^{2}H, C^{3}H, Ph), 7.74 (d, 1H, C^{6}H, ^3J 8.0 Hz), 7.80–7.85 (m, 1H, C^{1}H), 8.01–8.09 (m, 1H, C^{4}H). ^{13}C NMR, δ: 110.0 (*C*HPh), 114.2 (C^9), 120.3, 120.7, 121.7 (C^1, C^4, C^6), 122.8, 122.9 (C^7, C^8), 126.9 (C^{11a}), 128.5, 129.6, 129.9 (C^2, C^3, C^4, Ph), 128.6, 130.2 (C^2, C^3, C^5, C^6, Ph), 129.2, 132.5, 135.1, 140.7 (C^{11}, C^{4a}, C^{9a}, C^1, Ph), 148.8 (C^{5a}), 158.0 (C^{4b}). HRMS, *m*/*z*: 295.1230 [M + H]$^+$ (calc. for $C_{21}H_{14}N_2$, *m*/*z*: 295.1231).

For characteristics of compounds **4b**–**e**, see Online Supplementary Materials.

‡ *6-Arylbenzimidazo[2,1-*a*]isoquinolines* **5a**–**e** *(general procedure)*. A solution of *o*-diaminobenzene **2** (1 mmol) in anhydrous DMSO (2 ml) was slowly added to a solution of the corresponding aldehyde **1** (1 mmol) in DMSO (2 ml). Then, NH_4Br (39 mg, 0.4 mmol) was added. The mixture was stirred in the contact with dry air at room temperature for 24 h and thereafter was heated at 110–115 °C for 4–5 h. After cooling to room temperature, water (30 ml) and Et_2O (30 ml) 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 hexane–THF to give products **5a**–**e**.

This reaction, in conjunction with oxidative cyclization of aldehydes **1** with aromatic diamines **2** in DMSO in the presence of NH_4Br, represents a convenient one-pot approach to the fused isoquinolines from available starting compounds. Compared to known procedures which require application of transition metal catalysts, harsh conditions (lengthy heating at high temperatures) or toxic solvents (like nitrobenzene), it is characterized by low cost of reagents and simple experimental technique.

In summary, we have developed new one-pot transition metal-free syntheses of 11-arylmethylidene-11*H*-isoindolo[2,1-*a*]benzimidazoles and 6-arylbenzimidazo[2,1-*a*]isoquinolines from *o*-alkynylbenzaldehydes and *o*-diaminobenzenes in DMSO. An important feature of this approach is opportunity to perform 5-*exo*-*dig* or 6-*endo*-*dig* ring closure at the final stage by simple modification of reaction conditions.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.05.004.

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6-Phenylbenzimidazo[2,1-a]isoquinoline **5a** was prepared from aldehyde **1a** and diamine **2a** in 80% yield. ^{1}H NMR, δ: 6.49 (d, 1H, C^{8}H, ^3J 8.4 Hz), 6.88 (s, 1H, C^{5}H), 7.00 (dd, 1H, C^{9}H, ^3J 8.4 Hz, ^3J 7.7 Hz), 7.39 (dd, 1H, C^{10}H, ^3J 8.2 Hz, ^3J 7.7 Hz), 7.54–7.74 (m, 8H, C^{2}H, C^{3}H, C^{4}H, Ph), 8.01 (d, 1H, C^{11}H, ^3J 8.2 Hz), 8.85–8.95 (m, 1H, C^{1}H). ^{13}C NMR, δ: 112.6, 114.1 (C^5, C^8), 119.5 (C^{11}), 121.2, 124.2 (C^9, C^{10}), 122.7 (C^{12b}), 125.0, 126.6, 127.8, 129.8, 130.1 (C^1, C^2, C^3, C^4; C^4, Ph), 128.9, 129.3 (C^2, C^3, C^5, C^6, Ph), 130.6, 131.5, 134.5 (C^{7a}, C^{11a}; C^1, Ph), 137.4 (C^6), 144.0 (C^{4a}), 148.1 (C^{12a}). HRMS, *m*/*z* 295.1226 $[M+H]^+$ (calc. for $C_{21}H_{14}N_2$, *m*/*z*: 295.1231). These data are in good agreement with the reported ones.[17]

For characteristics of compounds **5b**–**e**, see Online Supplementary Materials.

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