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DBU as a scaffold for the synthesis of [1,3]oxazolo[2′,3′:2,3]pyrimido-[1,2-*a*]azepines: annulation with aromatic cyanopropargylic alcohols

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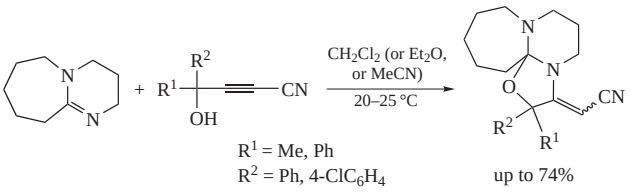
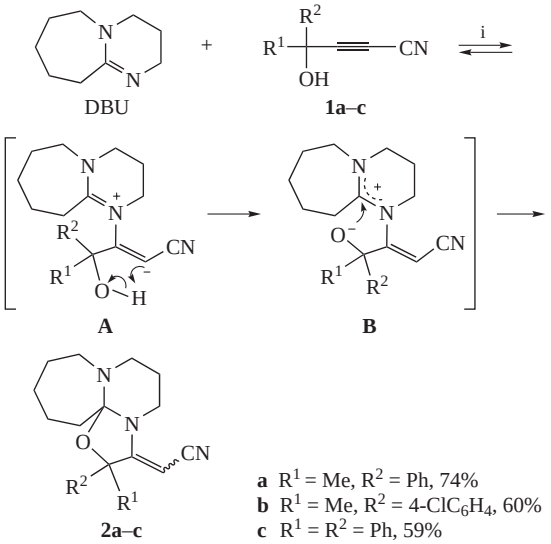
Organic superbase DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene, is readily annulated with aromatic cyanopropargylic alcohols under mild conditions (CH_2Cl_2, 20–25 °C, 30 min) to afford new 3-cyanomethylideneperhydro[1,3]oxazolo[2′,3′:2,3]pyrimido-[1,2-*a*]azepines.



1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is widely applied in organic syntheses[1] mostly mentioned as a non-nucleophilic, sterically hindered strong base. This concept has been revised after appearance of reports on incorporation of DBU into molecules through nucleophilic reactions.[2] Compared to a total number of reports on nucleophilic behavior of DBU, there were just a few publications[3] concerning its interaction with acetylenic moiety, wherein it was shown that DBU was capable of annulating with alkynoates (dimethyl acetylenedicarboxylate,[3(a)] methyl perfluoroalk-2-ynoates[3(b),(c)] and methyl propiolate[3(d)]) to give fused tricyclic derivatives such as diazabenzoazulene[3(a)] and diazacycloheptanaphthalenes.[3(b)–(d)] Recently we reported the annulation of DBU with aliphatic propargylic alcohols bearing electron-withdrawing groups (acyl, alkoxycarbonyl, cyano) at the triple bond, which led to functionalized perhydro[1,3]oxazolo[2′,3′:2,3]pyrimido-[1,2-*a*]azepines in 58–93% yields.[4] The similar heterocyclic systems are of high medicinal relevance as they are principal structural units of compounds with antitumor[5] and antimicrobial[6] activities. The hexahydropyrimidine moieties are frequently met in alkaloids (*e.g.* verbamethine and verbametrine[7]) and compounds with anticancer,[8] anti-inflammatory,[9] analgesic,[9(a),(b)] antibiotic,[8(b)] antianginal,[10] anxiolytic[11] and antidepressant[11] activities.

This communication deals with the extension of such a reaction employing cyanopropargylic alcohols **1** with aromatic substituents (Scheme 1).† A major goal was to obtain 2-arylated systems **2**, which should considerably improve the synthetic potential of this approach. The experiments have shown that the annulation of DBU with aromatic substrates **1a–c** occurs though more sluggishly than that with corresponding aliphatic congeners, despite the starting acetylenes **1** are consumed faster.

Indeed, when cyanopropargylic alcohol **1a** is fed to the solution of DBU in MeCN at room temperature (as previously), the reaction mixture turns brown and the band of the triple bond at 2295–2279 cm^{-1} (IR monitoring) disappears within 10 min. Despite the complete conversion of cyanopropargylic alcohol **1a**, the yield of the annulated product **2a** is just 31% (Table 1, entry 1). Note that, under the same conditions, full aliphatic analogues form the corresponding products in 58–82% yields.[4] As shown in case of annulation of DBU with **1a**, in less polar



Scheme 1 *Reagents and conditions:* i, CH_2Cl_2, 20–25 °C, 30 min.

† Aromatic cyanopropargylic alcohols **1a–c** were prepared according to published methods.[13]

General procedure for the synthesis of compounds **2a–c**. Cyanopropargylic alcohol **1a–c** (1 mmol) in CH_2Cl_2 (4 ml) was added dropwise to a solution of DBU (0.152 g, 1 mmol) in CH_2Cl_2 (4 ml) over 10 min. The mixture was stirred at 20–25 °C for 20 min. Solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (SiO_2, eluent: hexane–Et_2O, 1:1) to give tricyclic products **2a–c**.

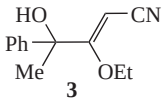
*2-[2-Methyl-2-phenylhexahydro-5*H,9H-*[1,3]oxazolo[2',3':2,3]-pyrimido[1,2-*a*]*azepin-3(2*H)*-yliden]acetonitrile* **2a**: yield 0.239 g (74%), light yellow oil. Diastereomer ratio, 1:2. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ: *Z*-isomer: 1.37 (m, 1H, $C^{13}H_2$), 1.52 (m, 1H, $C^{11}H_2$), 1.54 (m, 1H, $C^{12}H_2$), 1.64 (m, 1H, $C^{14}H_2$), 1.71 (m, 1H, $C^{12}H_2$), 1.76 (m, 2H, C^5H_2, $C^{13}H_2$), 1.75, 1.81 (s, 3H, Me), 1.83 (m, 1H, $C^{11}H_2$), 2.00 (m, 1H, C^5H_2), 2.13 (m, 1H, $C^{14}H_2$), 2.78 (m, 1H, $C^{10}H_2$), 2.90 (m, 1H, C^4H_2), 2.92 (m, 1H, C^4H_2), 3.20 (m, 1H, $C^{10}H_2$), 3.21 (m, 1H, C^6H_2), 3.46, 3.70 (s, 1H, =CH), 4.59, 4.60

Table 1 The solvent effect on the yield of the annulated product **2a** in the reaction between DBU and **1a**.

Entry	Solvent	*T*/°C	*t*/min	Yield (%)
1	MeCN	20–25	10	31
2	MeCN	–5–0	15	35
3	Et_2O	20–25	30	70
4	CH_2Cl_2	20–25	30	74
5	EtOH	20–25	10	–[a]

[a]Adduct **3** was isolated in 29% yield.

solvent (Et_2O, CH_2Cl_2) the reaction proceeds slower (30 min), whereas the yield of target product **2a** rises to 70–74% (entries 3, 4). In ethanol, no annulated product is formed but nucleophilic addition of ethanol at the triple bond of **1a** occurs to give adduct **3** (entry 5). In this case, DBU plays a role of a basic catalyst.



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Consequently, all further experiments were carried out in the CH_2Cl_2 solution at room temperature for 30 min. The best results of the DBU annulation with aromatic cyanopropargylic alcohols **1a**–**c** are outlined in Scheme 1.

The annulation leads exclusively to *Z*-isomers of **2a**–**c** that follows from ^{1}H NMR spectra of the crude products. This stereoselectivity is expected from the known *trans*-mode of concerted nucleophilic addition to acetylenes.[12] On storing at room temperature, the *Z*-isomers of **2a**,**b** are gradually transformed into the *E* ones, thus evidencing the kinetic cause of the stereoselectivity. Notably, adduct **2c** was not isomerized even during 2 months, probably due to steric screening of the double bond (since *E*,*Z*-isomerization in this case may occur *via* the reversible nucleophilic addition of trace water to electron deficient double bond).

^{1}H NMR spectra of adducts **2a**–**c** contain signals of the =CHCN fragment at 3.44–3.88 ppm. In their ^{13}C NMR spectra, the olefinic carbon (=*C*HCN) resonates in the region of 53.9–58.7 ppm and the signals of the C^2 carbon appear at 107.7–109.7 ppm. The doubling of the ^{1}H and ^{13}C NMR signals for products **2a**,**b** results from the two diastereomers (the ratio is 1 : 2 for **2a**, 1 : 1.5 for **2b**). The configurational assignment and substituent location for compounds **2a**–**c** were based on ^{1}H, ^{13}C, ^{15}N and 2D (NOESY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C and ^{1}H–^{15}N HMBC) NMR spectroscopy data. In the 2D NOESY spectra, the cross-peaks between the olefinic proton and protons of methyl or aryl groups for *Z*-isomer and between the olefinic proton and protons at C^6 atom for *E*-isomer were observed [Figure 1(*a*)]. Additional configurational assignment for the olefinic fragment is the comparison of vicinal coupling constants $^3J_{C^9,H}$ and $^3J_{N^7,H}$. The values of vicinal $^3J_{C^9,H}$ in the range of 2.0–4.1 Hz and $^3J_{N^7,H}$ near 8.7–8.8 Hz correspond to the *cis*-position of olefinic proton with respect to the C^9, *i.e.* to *Z*-configuration of adducts **2**. For *E*-isomers, coupling constants $^3J_{C^9,H}$ and $^3J_{N^7,H}$ are 7.5–8.2 and 3.2–3.5 Hz, respectively [Figure 1(*b*)].

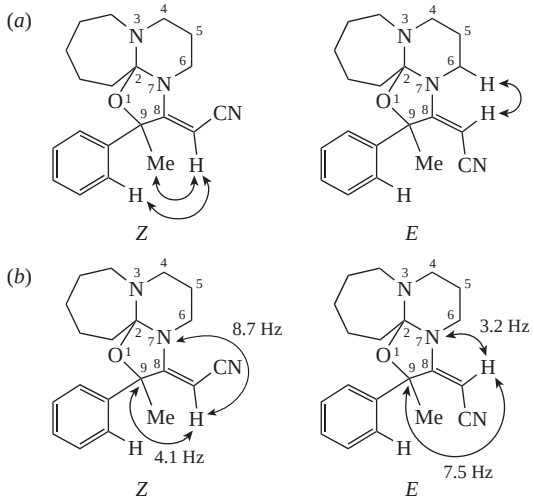

Figure 1 Cross-peaks in the (*a*) NOESY and (*b*) HMBC spectra of the adduct **2a**.

As previously[4] shown, the annulation of DBU with aromatic cyanopropargylic alcohols **1** proceeds *via* nucleophilic attack of the amidine group of DBU at the triple bond. Then, the proton transfer from hydroxyl of intermediate **A** quenches the carbanionic center, thus forming thermodynamically more stable zwitterion **B**. The latter attacks the 2-position of the DBU scaffold to finish the annulation (see Scheme 1).

As follows from the experiments, specific peculiarities of the DBU/aromatic cyanopropargylic alcohol annulation, compared to the reaction with aliphatic congeners, are a slower process rate and accelerating effect of a less polar solvent. According the above mechanism, this is apparently due to a stronger screening of the anionic oxygen centre site in intermediate **B** and its deactivation by the dipole–dipole interaction with the molecules of the polar solvent (MeCN, μ = 3.92 D). Under this condition, the competitive polymerization of acetylene **1** becomes predominant, that is supported by the ^{1}H NMR spectra of the isolated polymers (no DBU signals are detectible wherein). Consequently, in the media of a moderate polarity (Et_2O, CH_2Cl_2, μ = 1.15 and 1.60 D, respectively) the annulation facilitates, while polymerization of the acetylene is suppressed.

In conclusion, the annulation of DBU with aromatic cyanopropargylic alcohols represents an efficient and practical synthesis of perhydro[1,3]oxazolo[2′,3′:2,3]pyrimido[1,2-*a*]azepines with aromatic substituents. The method is based on the available starting materials, simple one-step operation and does not require any metal catalyst. The synthesized compounds are novel promising drug precursors and rewarding building blocks for further construction of the molecular complexity.

(m, 1H, C^6H_2), 7.25 (m, 1H, *p*-H_{Ph}), 7.30 (m, 2H, *m*-H_{Ph}), 7.44, 7.58 (m, 2H, *o*-H_{Ph}). *E*-isomer: 1.40 (m, 2H, $C^{13}H_2$, $C^{11}H_2$), 1.56 (m, 1H, C^5H_2), 1.59 (m, 1H, $C^{12}H_2$), 1.75 (m, 1H, $C^{13}H_2$), 1.79 (m, 1H, $C^{12}H_2$), 1.80 (m, 1H, $C^{14}H_2$), 1.83 (m, 1H, C^5H_2), 1.85 (m, 1H, $C^{11}H_2$), 2.00, 2.12 (s, 3H, Me), 2.36 (m, 1H, $C^{14}H_2$), 2.47 (m, 1H, $C^{10}H_2$), 2.80 (m, 1H, C^4H_2), 2.98 (m, 1H, C^4H_2), 3.10 (m, 1H, $C^{10}H_2$), 3.34 (m, 1H, C^6H_2), 3.39, 3.42 (m, 1H, C^6H_2), 3.76, 3.89 (s, 1H, =CH), 7.25 (m, 1H, *p*-H_{Ph}), 7.30 (m, 2H, *m*-H_{Ph}), 7.52, 7.73 (m, 2H, *o*-H_{Ph}). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: *Z*-isomer: 20.7, 21.2 ($C^{12}H_2$), 23.1, 24.3 (C^5H_2), 24.5, 26.3 ($C^{11}H_2$), 26.7, 27.2 ($C^{13}H_2$), 27.8, 28.7 (Me), 35.0, 36.9 ($C^{14}H_2$), 39.9, 41.2 (C^6H_2), 45.4, 45.9 (C^4H_2), 47.1, 48.6 ($C^{10}H_2$), 53.9, 55.4 (=CH), 86.5, 87.7 (C^9), 107.7, 108.7 (C^2), 119.6, 119.9 (CN), 125.3, 126.4 (*o*-C_{Ph}), 128.2, 128.3 (*m*-C_{Ph}), 127.9, 128.0 (*p*-C_{Ph}), 143.2, 143.5 (*i*-C_{Ph}), 163.7, 164.0 (C^8). *E*-isomer: 20.4, 20.8 ($C^{12}H_2$), 22.0, 23.8 (C^5H_2), 23.9, 25.3 ($C^{11}H_2$), 24.6, 25.9 (Me), 26.0, 26.7 ($C^{13}H_2$), 35.1, 36.5 ($C^{14}H_2$), 40.7, 41.3 (C^6H_2), 45.9, 46.1 (C^4H_2), 46.5, 47.5 ($C^{10}H_2$), 54.9, 57.0 (=CH), 86.8, 87.6 (C^9), 106.1, 106.9 (C^2), 119.7 (CN), 124.9, 126.4 (*o*-C_{Ph}), 127.6, 127.9 (*p*-C_{Ph}), 128.1, 128.2 (*m*-C_{Ph}), 141.6, 142.0 (*i*-C_{Ph}), 165.5, 166.7 (C^8). ^{15}N NMR (40.6 MHz, $CDCl_3$) δ: *Z*-isomer: –123.4 (CN), –259.7 (N^7), –317.3 (N^3). *E*-isomer: –123.4 (CN), –261.6 (N^7), –317.3 (N^3). IR (ν/cm^{-1}): 3059, 2930, 2862, 2752, 2722, 2691, 2194, 1613, 1441, 1400, 1360, 1311, 1255, 1229, 1153, 1124, 1089, 1039, 963, 869, 821, 762, 700, 651. MS (EI), *m*/*z* (%): 324 (29) $[M+H]^+$, 323 (100) $[M]^+$, 295 (20), 294 (78), 283 (14), 280 (25), 268 (10), 267 (28), 253 (16), 252 (12), 210 (11), 197 (13), 183 (12), 167 (11), 155 (10), 154 (14), 140 (15), 139 (16), 128 (12), 127 (14), 115 (17), 98 (18), 97 (12), 96 (14), 77 (15), 70 (16), 69 (16), 68 (11), 56 (19), 55 (23), 44 (11), 43 (17), 42 (33), 41 (43). Found (%): C, 74.51; H, 7.84; N, 12.72. Calc. for $C_{20}H_{25}N_3O$ (%): C, 74.27; H, 7.79; N, 12.99.

For characteristics of compounds **2b**,**c**, see Online Supplementary Materials.

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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.2018.03.004.

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