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Reactions of 3,4-dihydroisoquinolines and dihydrothieno[3,2-*c*]pyridines with benzyne

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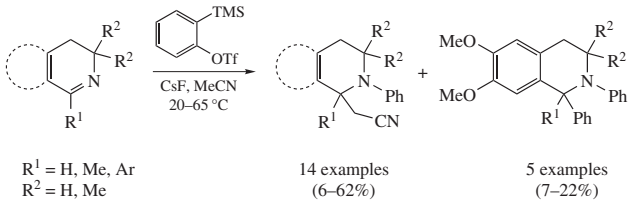
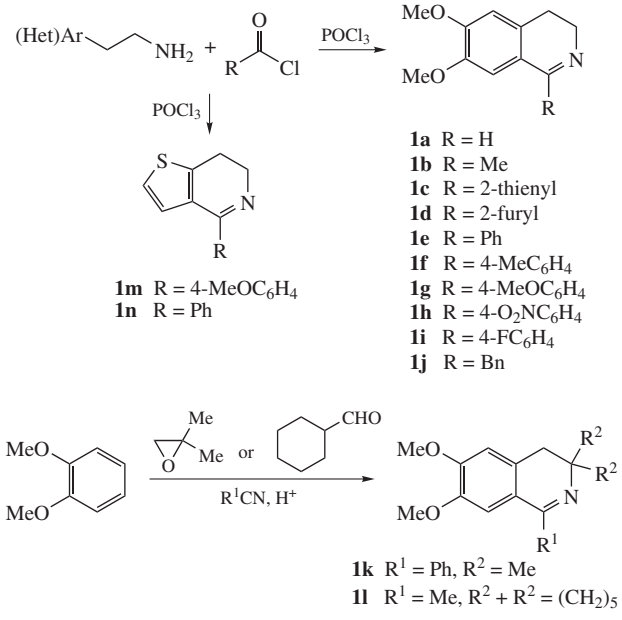
Cyanomethyl-substituted tetrahydroisoquinolines and tetrahydrothieno[3,2-*c*]pyridines were synthesized by multicomponent reaction of the dihydro analogues of aforesaid systems with benzyne and acetonitrile. The products obtained relate to alkaloids of isoquinoline family of 1,2,3,4-tetrahydro level.



Isoquinolines and derivatives thereof represent a class of organic compounds with wide range of biological activity,[1,2] most of them being used in medicine. Among isoquinoline alkaloids those with dihydro- and especially tetrahydroisoquinoline core are prevalent.[3] Moreover, such compounds are often applied as building blocks in organic synthesis. Most approaches to functionalized tetrahydroisoquinolines are based on the trapping of iminium salts with nucleophiles[4,5] or organometallic compounds[6–8] alongside with oxidative C–H functionalization.[9–11] In recent decades, the chemistry of arynes received a widespread use due to their ability to react with a variety of heterocycles and even with neutral nucleophiles.[12–17] The multicomponent reactions (MCR) with the involvement of arynes are often employed for the functionalization of heterocyclic compounds[18–22] especially of (iso)quinolines and pyridines as well as for the synthesis of complex structures.[23–26]

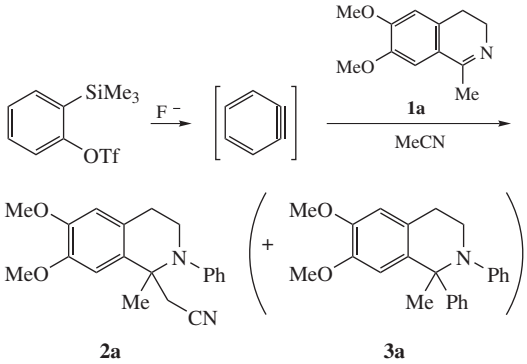


Scheme 1

Herein we disclose an approach towards 1,1-disubstituted tetrahydroisoquinolines and 4,4-disubstituted tetrahydrothieno-[3,2-*c*]pyridines bearing cyanomethyl group at C-1 and C-4 position, respectively, based on MCR of dihydro analogues of the aforesaid compounds with aryne and acetonitrile.

The starting 3,4-dihydroisoquinolines **1a–j** and dihydrothieno-[3,2-*c*]pyridines **1m**,**n** were obtained by the Bischler–Napieralski method (Scheme 1). Dihydroisoquinolines **1k**,**l** were synthesized by the Ritter-type reactions.[27]

We started our investigation with the model reaction between 1-methyl substituted dihydroisoquinoline **1a** and benzyne in the presence of CsF (Scheme 2, Table 1). It was found that the reaction proceeded slowly at room temperature even with twofold excess



Scheme 2

Table 1 Optimization of addition of benzyne to tetrahydroisoquinoline **1a** in MeCN.

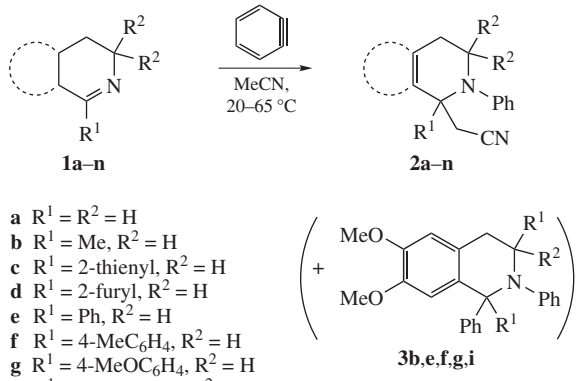
Entry	Promoter	*T*/°C	Reaction time	Yield of **2a** (%)
1	CsF	20	3 days	15
2	CsF	65	24 h	30
3	CsF	125[a]	5 min	41 (+7% of **3a**)
4	TBAT[b]	20	24 h	–

[a] Under MW irradiation. [b] Tetrabutylammonium difluoro(diphenyl)silicate.

of aryne: the target 1-cyanomethylated derivative **2a** was isolated in 15% yield while most of the starting dihydroisoquinoline was recovered (see Table 1).

Raising the temperature up to 65 °C accelerates the reaction leading to target compound **2a** in 30% yield. The use of microwave irradiation significantly reduces the reaction time and increases the yield up to 41%. However, higher temperature provoked the formation of compound **3a**, a side product of double aryne insertion, lacking cyanomethyl grouping. Despite of substantial advantage of microwave irradiation, this procedure did not work for 1-furyl and some 1-aryl substituted isoquinolines. Although the TBAT-promoted reaction occurred smoothly, the target product could not be completely separated from this reagent even after several purifications. Therefore, in our further investigation we used moderate heating unless indicated otherwise (Table 2). Our attempts to involve other CH-acids such as propanedinitrile, nitromethane, and nitroethane in this reaction were unsuccessfull. Inseparable multicomponent mixtures and resins were mostly obtained. None of compounds reacted with malononitrile even after boiling in toluene for a week with tenfold excess of benzyne precursor.

As can be seen from Table 2, the better yields of products **2** (Scheme 3) were achieved when the reactant had no substituent at the C-1 position of isoquinoline core (entry 2) or was deprived of electron-withdrawing group in such an aromatic substituent (compare entries 4–7 with 8). The reaction with **1h** (entry 8) afforded a considerable amount of tar products, none of them having been major. It is noteworthy that the presence of strong electron-donating group in the C-1-positioned aryl substituent favors formation of both the target compounds and side-products (entry 7). In cases of thienopyridines **1m**,**n**, the reaction proceeded at moderate heating smoothly and faster as compared to isoquinoline analogues.

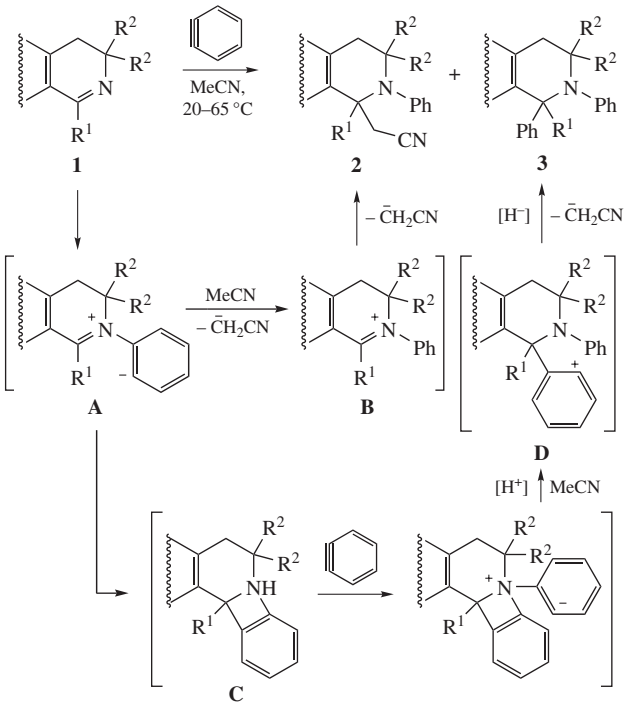


a $R^1 = R^2 = H$
b R^1 = Me, $R^2 = H$
c R^1 = 2-thienyl, $R^2 = H$
d R^1 = 2-furyl, $R^2 = H$
e R^1 = Ph, $R^2 = H$
f R^1 = 4-MeC_6H_4, $R^2 = H$
g R^1 = 4-$MeOC_6H_4$, $R^2 = H$
h R^1 = 4-$O_2NC_6H_4$, $R^2 = H$
i R^1 = 4-FC_6H_4, $R^2 = H$
j R^1 = Bn, $R^2 = H$
k R^1 = Ph, R^2 = Me
l R^1 = Me, $R^2 + R^2 = (CH_2)_5$
m R^1 = 4-$MeOC_6H_4$, $R^2 = H$
n R^1 = Ph, $R^2 = H$

Scheme 3

We suppose that the reaction starts with addition of dihydroisoquinoline at the triple bond of aryne resulting in zwitter-ion **A** (Scheme 4) which can further eliminate hydrogen atom from acetonitrile giving intermediate **B**. The nucleophilic attack of thus generated cyanomethyl anion at C-1 position of dihydroisoquinoline leads to 1-R-1-cyanomethyl derivatives. The formation of diphenyl substituted products **3b**,**e**,**f**,**g**,**i** possibly occurs through the intramolecular [2+2]-cycloaddition in the zwitter-ion **A**[28–30] to give intermediate **C**. Its subsequent reaction with the second molecule of aryne and acetonitrile affords (as a hydrogen source) products of double benzyne addition. The cyanomethyl anion serves as cryptobase for cationic intermediate **D**.

The structure of compound **2d** was unambiguously confirmed by X-ray analysis (Figure 1).† Its tetrahydropyrimidine ring adopts a slightly distorted *sofa* conformation. The N(2) atom has a



Scheme 4

Table 2 Reaction of 3,4-dihydroisoquinolines and dihydrothieno[3,2-*c*]-pyridines with benzyne.

Entry	Conditions	Reactant **1**	Product **2**	By-product
1	MW, 125 °C, 5 min	**1a**	**2a** (41%)	**3a** (7%)
2	20 °C, 24 h	**1b**	**2b** (58%)	–
3	65 °C, 5 days	**1c**	**2c** (45%)	–
4	65 °C, 6 days	**1d**	**2d** (49%)	–
5	65 °C, 1 month	**1e**	**2e** (55%)	**3e** (13%)
6	20 °C, 2 days	**1f**	**2f** (50%)	**3f** (9%)
7	65 °C, 4 days	**1g**	**2g** (61%)	**3g** (22%)
8	65 °C, 1 month	**1h**	**2h** (6%)	–
9	65 °C, 5 days	**1i**	**2i** (50%)	**3i** (10%)
10	65 °C, 2 days	**1j**	**2j** (35%)	**4** (10%)
11	20 °C, 5 days	**1k**	**2k** (44%)	–
12	20 °C, 5 days	**1l**	**2l** (38%)	–
13	65 °C, 24 h	**1m**	**2m** (45%)	–
14	65 °C, 24 h	**1n**	**2n** (62%)	–

† *Crystal data for* **1**: $C_{34}H_{24}N_2O_6Zn$ (M = 621.92) monoclinic, space group $P2_1/c$, at 293 K: a = 8.0301(9), b = 21.012(2) and c = 17.3295(17) Å, β = 112.532(4)°, V = 2700.8(5) Å^3, Z = 4, d_{calc} = 1.530 g cm^{-3}, μ(MoKα) = = 0.963 mm^{-1}, F(000) = 1280. Total of 13 255 reflections were measured and 4756 independent reflections (R_{int} = 0.0438) were used in a further refinement, which converged to wR_2 = 0.1123 and GOF = 0.948 for all independent reflections [R_1 = 0.0469 was calculated against F for 3458 observed reflections with $I > 2\sigma(I)$]. The measurements were made on a Bruker Apex Smart CCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using a full-matrix least-squares procedure based on F^2.[16] The hydrogen atom positions were fixed geometrically at calculated distances and allowed them to ride on the parent atoms.

CCDC 885118 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

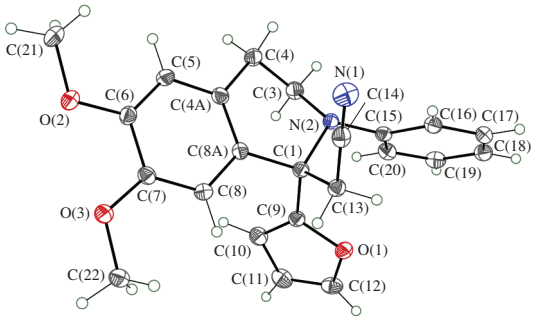
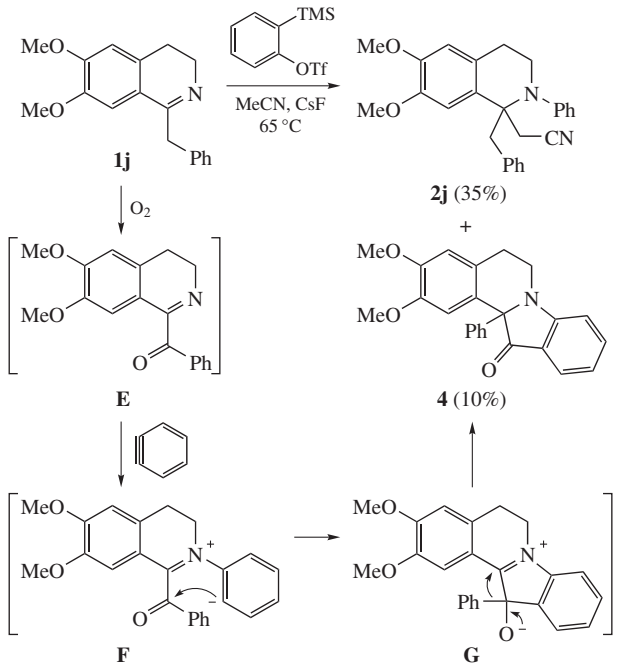


Figure 1 The X-ray crystal diffraction of compound **2d**.

trigonal-pyramidal geometry. The phenyl substituent occupies the sterically favorable equatorial position. The both methoxy groups are almost coplanar to the central benzene ring.

Interestingly, in case of 1-benzyl substituted dihydroisoquinoline **1j**, along with expected 1-cyanomethylated derivative **2j**, indoloisoquinoline **4** was obtained in 10% yield (Scheme 5).



Scheme 5

Apparently, its formation occurs due to the presence of methylene fragment in the reactant, which is easily oxidized by accidental oxygen during the reaction leading to ketone **E**. The latter can react with aryne giving zwitter-ion **F** which undergoes further cyclization into intermediate **G**. Intramolecular nucleophilic substitution in **G** followed by phenyl anion migration to the C-1 position of isoquinoline moiety results in indolo-[2,1-*a*]isoquinolinone **4**.

This hypothesis has been confirmed by reaction of 1-aroyl substituted dihydroisoquinolines with arynes.[31]

In summary, we developed an approach toward 1- and 4-functionalized tetrahydroisoquinolines and tetrahydrothienopyridines, respectively, based on MCR of dihydroisoquinolines or thienopyridines with benzyne and acetonitrile used both as a solvent and as a third component. These compounds are of interest from the synthetic point of view due to the presence of cyano group that can be readily modified for further transformations. Benzyl substituted dihydroisoquinoline gave a product of aryne insertion along with the expected 1-cyanomethyl substituted tetrahydroisoquinoline.

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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.2017.09.026.

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