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Efficient Synthesis of 3-Aryl(hetaryl)-1,5,3-dioxazepanes Involving Catalysts Containing Sm and Co

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Abstract—Efficient synthetic procedure was developed for *3*-aryl(hetaryl)-1,5,3-dioxazepanes consisting in the transamination of 3-*tert*-butyl-1,5,3-dioxazepane with arylamines and also by the reaction of 1,2-ethanediol with *N,N*-bis(methoxymethyl)aryl(hetaryl)amines in the presence of catalytic amounts of Sm and Co compounds.

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Oxazepane derivatives are widely used in the medicine as substances exhibiting analgesic, antipyretic, sedative [1, 2], anticancer [3], and fungicidal [4, 5] action. Quite a number of papers treats the problems of the synthesis of *O,N*-containing five- and six-membered heterocycles [6–8], whereas scarce information exist on the selective synthesis of *N*-substituted 1,5,3-dioxazepanes [9–11]. *N*-Alkyl(cycloalkyl, benzyl)-1,5,3-dioxazepanes are obtained by heating alkyl(cycloalkyl, benzyl)amines with paraformaldehyde and 1,2-ethylene glycol in aromatic solvents [9–11]. To the time of the start of our study no literature data existed on the selective synthesis of *3*-aryl(hetaryl)-1,5,3-dioxazepanes.

By the analogy of the previously investigated transamination of *3*-methyl-1,3,5-dithiazinane with aniline giving *3*-phenyl-1,3,5- dithiazinane [12], we carried out the reaction of primary arylamines with *3*-*tert*-butyl-1,5,3-dioxazepane in the presence of catalysts based on transition and rare earth metals presuming the possibility of the replacement of the nitrogen atom in the molecule of *3*-*tert*-butyl-1,5,3-dioxazepane by the transamination leading to the formation of the corresponding *3*-aryl-1,5,3-dioxazepanes in the presence of catalytic amounts of Sm and Co complexes.

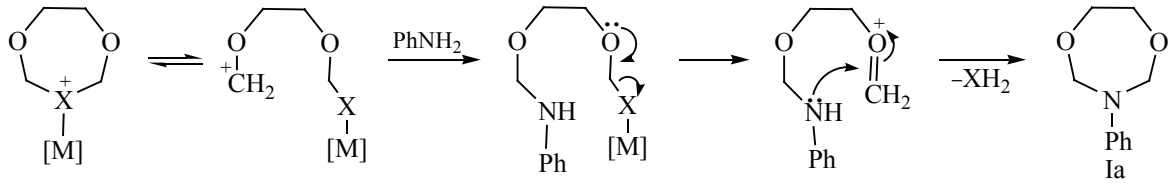
Preliminary experiments have shown that noncatalytic reaction of aniline with an equimolar quantity of *3*-*tert*-butyl-1,5,3-dioxazepane (~20°C, 3 h, solvent chloroform) afforded *3*-phenyl-1,5,3-dioxazepane (**Ia)** in less than 8% yield. The yield of compound **Ia** may be increased if the transamination is carried out in the presence of catalysts based on the salts and complexes of Cu, Pd, Co, Zr, Ti, Hf, V, Fe, Sm [12], where the most active are $Sm(NO_3)_3 \cdot 6H_2O$ and $CoCl_2$. Under the action of these catalysts (5 mol%, ~20°C, 3 h, solvent $CHCl_3$) the transamination proceeds highly selectively (~100%) with the formation of *N*-phenyl-1,5,3-dioxazepane (**Ia**) in 70 and 65% yields respectively. The significant acceleration of the reaction is apparently due to the coordination of the nitrogen atom of the molecule of the initial *3*-*tert*-butyl-1,5,3-dioxazepane to the central atom of the catalyst [13].

The probable route [14, 15] of the catalytic transamination of *3*-*tert*-butyl-1,5,3-dioxazepane under the action of aniline involves a stage of the opening of the initial heterocycle, the nucleophilic addition of aniline to the carbocation and the intramolecular cyclization affording *3*-phenyl-1,5,3-dioxazepane (**Ia**) (Scheme 1).

In the ^{1}H NMR spectrum of compound **Ia** the proton signals appear as narrow singlets in the region of 4.80 ($H^{2,4}$) and 3.08 ppm ($H^{6,7}$) indicating the fast ring inversion in the NMR time scale. In the ^{13}C NMR spectrum the dioxazepane carbon atoms give rise to signals δ 54.92 and 35.78 ppm.

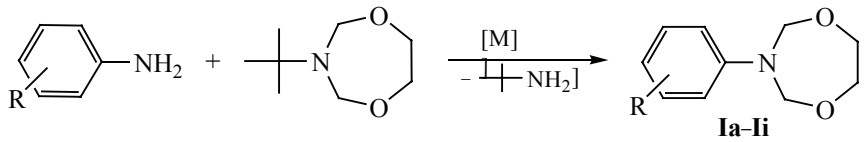
The structure of the initial arylamine does not considerably affect the yield of of compound **I**. In the reaction of

Scheme 1.



X = *t*-BuN; [M] = $Sm(NO_3)_3 \cdot 6H_2O$, $CoCl_2$.

Scheme 2.



Ia–Ii

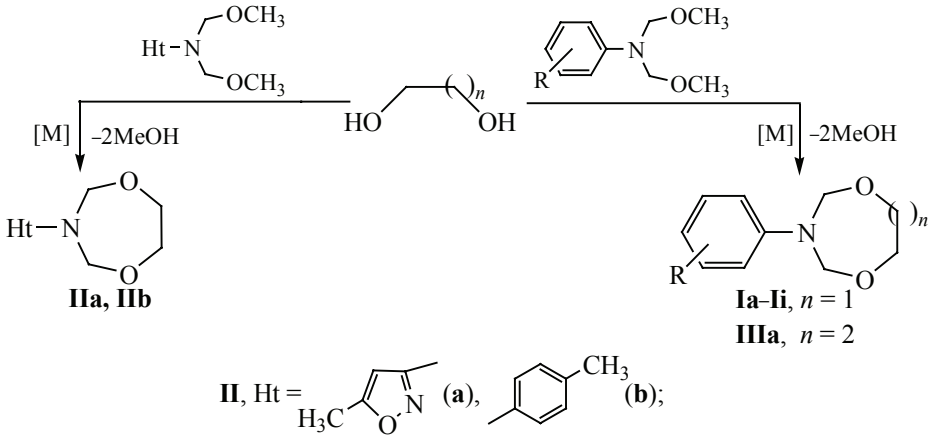
R = H (**a**), *m*-CH_3 (**b**), *p*-CH_3 (**c**), *o*-OCH_3 (**d**), *m*-OCH_3 (**e**), *p*-OCH_3 (**f**), *o*-NO_2 (**g**), *m*-NO_2 (**h**), *p*-NO_2 (**i**); [M] = $Sm(NO_3)_3 \cdot 6H_2O$, $CoCl_2$.

o-, m-, and *p*-nitro-, *o-, m-,* and *p*-methoxy-, and also *m*- and *p*-methylanilines with equimolar quantity of *3-tert*-butyl-1,5,3-dioxazepane (5 mol% of $Sm(NO_3)_3 \cdot 6H_2O$, ~20°C, 3 h) the corresponding *3*-aryl-1,5,3-dioxazepanes **Ia–Ii** were formed in 60–70% yields (Scheme 2).

The attempt to transaminate the *3-tert*-butyl-1,5,3-dioxazepane with hetarylamines (3-amino-5-methylisoxazole, 2-amino-, 3-amino-, 2-amino-4-methyl-, 2-aminoo-5-methylpyridine) failed.

To develop an efficient synthetic procedure for *3*-hetaryl-1,5,3-dioxazepanes we examined the reaction of 1,2-ethanediol with *N,N*-bis(methoxymethyl)-*N*-hetarylamines. Whereas the aminomethylation of C,H- and S,H-acids with alkoxymethylamines results in acyclic amines and aminosulfides due to the formation of C–C and C–S bonds [16], it is expectable that the aminomethylation of 1,2-ethanediol with *N,N*-bis-(alkoxymethyl)amines would lead to the corresponding dioxazepanes by the simultaneous formation of two C–O bonds. The performed experiments showed that under the chosen conditions [5 mol% of $Sm(NO_3)_3 \cdot 6H_2O$, 20°C, 0.5 h] only *N,N*-bis(methoxymethyl)-*N*-hetarylamines prepared from 3-amino-5-methylisoxazole and 2-amino-5-methylpyridine readily reacted with 1,2-ethanediol to give selectively *3*-hetaryl-1,5,3-dioxazepanes **IIa, IIb** in 60 and 64% yields (Scheme 3). Compounds **IIa, IIb** are

Scheme 3.



IIa, IIb

Ia–Ii, *n* = 1

IIIa, *n* = 2

II, Ht = (**a**), (**b**);

R = H (**a**), *m*-CH_3 (**b**), *p*-CH_3 (**c**), *o*-OCH_3 (**d**), *m*-OCH_3 (**e**), *p*-OCH_3 (**f**), *o*-NO_2 (**g**), *m*-NO_2 (**h**), *p*-NO_2 (**i**); [M] = $Sm(NO_3)_3 \cdot 6H_2O$ for **Ia–Ii, IIa,IIb**, zeolites 0.96 HY-BS for **IIIa**.

not formed without catalyst.

The developed procedure of the cycloaminomethylation of ethylene glycol with *N,N*-bis(methoxy-methyl) hetarylamines made it possible to extend this reaction to *N,N*-bis(methoxymethyl)-*N*-arylamines (aryl = Ph, *m*- and *p*-methyl-, *o-, m-,* and *p*-methoxy-, *o-, m-,* and *p*-nitrophenyl) and to obtain *N*-aryl-1,5,3- dioxazepanes **Ia–Ii** in 80–89% yields (Scheme 3). We attempted to try this procedure for a selective synthesis of dioxazocanes and dioxazonanes by the reaction of *N,N*-bis(methoxymethyl)-*N*-arylamines with 1,3-propanediol and 1,4-butanediol, and only in the presence of zeolites of the grade 0.96HY-BS (5 wt%) *N,N*-bis(methoxymethyl)-*N*-phenylamine reacted with 1,3-propanediol in $CHCl_3$ at ~60°C furnishing 3-phenyl-1,5,3-dioxazocane (**IIIa**) in 40% yield (Scheme 3).

Thus our research resulted in the development of an efficient synthesis of 3-aryl(hetaryl)-1,5,3-dioxazepanes by transamination of 3-*tert*-butyl-1,5,3-dioxazepane with arylamins and also by cycloaminomethylation of 1,2-ethanediol with *N,N*-bis(methoxy-methyl) aryl(hetaryl)amines under mild conditions in high yield and selectivity in the presence of catalysts based on Sm and Co compounds.

EXPERIMENTAL

The reaction progress was monitored by TLC on Silufol W-254 plates, eluent petroleum–ether EtOAc–$CHCl_3$, 5 : 1 : 1. The reaction products were analyzed by HPLC on a chromatograph Altex-330 (USA) equipped with a UV detector at the wavelength 340 nm. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance 400 (100.62 and 400.13 MHz respectively), solvent $CDCl_3$. GC-MS measurements were carried out on instruments Finnigan-4021 (glass capillary column 5000 × 0.25 mm, stationary phase HP-5, carrier gas helium, ramp from 50 to 300°C at a rate 5 deg/min, vaporizer temperature 280°C, ion source temperature 250°C, 70 eV) and Shimadzu QP-2010 Plus (capillary column Supelco PTE-5 30 m × 0.25 mm). For column chromatography silica gel KSK (100–200 μm) was utilized.

3-Aryl-1,5,3-dioxazepanes. ***a.*** **Transamination of 3-*tert*-butyl-1,5,3-dioxazepane with arylamines.** Into a Schlenk vessel placed on a magnetic stirrer was charged in an argon flow 10 mmol of 3-*tert*-butyl-1,5,3-dioxazepane [9] and 0.5 mmol of catalyst $Sm(NO_3)_3·6H_2O$ or $CoCl_2$, the mixture was stirred for 30 min, 5 ml of chloroform and 10 mmol of an appropriate arylamine was added, and the stirring was continued for 3 h at room temperature (~20°C).

b. **Reaction of *N,N*-bis(methoxymethyl)-*N*-arylamines with 1,2-ethanediol.** Into a Schlenk vessel placed on a magnetic stirrer was charged in an argon flow 10 mmol of *N,N-bis*(methoxymethyl)-*N*-aryl-amine [17] and 10 mmol of 1,2-ethanediol at room temperature (~20°C), 5 ml of chloroform, 0.5 mmol of catalyst $Sm(NO_3)_3·6H_2O$ was added, the mixture was stirred for 30 min.

3-Phenyl-1,5,3-dioxazepane (Ia). Yield 70% (*a*), 80% (*b*), mp 177–178°C. ^1H NMR spectrum, δ, ppm: 3.08 s (4H, CH_2), 4.80 s (4H, CH_2), 6.91–7.35 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 35.78 ($C^{6,7}$), 54.92 ($C^{2,4}$), 115.93 ($C^{9,13}$), 119.95 (C^{11}), 129.30 ($C^{10,12}$), 145.83 (C^{8}). Mass spectrum, *m/z* (I_{rel}, %): 179 $[M]^+$ (100), 159 $[C_9H_{13}NO]^+$ (30), 104 $[C_4H_{10}O_2]^+$ (15), 92 $[C_6H_6N]^+$ (45), 77 $[C_6H_5]^+$ (95).

3-(3-Methylphenyl)-1,5,3-dioxazepane (Ib). Yield 64% (*a*), 61% (*b*), mp 173–174°C. ^1H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 3.88 s (4H, CH_2), 4.89 s (4H, CH_2), 6.70–7.28 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 21.33 (C^{14}), 62.29 ($C^{6,7}$), 82.90 ($C^{2,4}$), 108.98 (C^{13}), 113.66 (C^{9}), 120.56 (C^{11}), 129.97 (C^{10}), 147.48 (C^{12}), 148.93 (C^{8}). Mass spectrum, *m/z* (I_{rel}, %): 193 $[M]^+$ (40), 180 $[C_{10}H_{15}NO_2]^+$ (15), 136 $[C_8H_{10}NO]^+$ (37), 106 $[C_7H_8N]^+$ (100), 104 $[C_4H_{10}O_2]^+$ (15), 92 $[C_6H_7]^+$ (32), 77 $[C_6H_5]^+$ (54).

3-(4-Methylphenyl)-1,5,3-dioxazepane (Ic). Yield 60% (*a*), 65% (*б*), mp 138–139°C. ^1H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 3.87 s (4H, CH_2), 4.44 s (4H, CH_2), 6.75–7.23 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 21.34 (C^{14}), 67.34 ($C^{6,7}$), 83.22 ($C^{2,4}$), 114.22 ($C^{9,13}$), 120.18 ($C^{10,12}$), 141.46 (C^{11}), 147.55 (C^{8}).

3-(2-Methoxyphenyl)-1,5,3-dioxazepane (Id). Yield 63% (*a*), mp 118–119°C. ^1H NMR spectrum, δ, ppm: 3.53–3.79 m (7H, CH_2, CH_3), 4.94 s (4H, CH_2), 6.37–7.23 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 55.23 (C^{15}), 68.77 ($C^{6,7}$), 80.88 ($C^{2,4}$), 102.01 (C^{10}), 104.98 (C^{13}), 109.21 (C^{12}), 130.06 (C^{11}), 146.93 (C^{8}), 160.61 (C^{9}). Mass spectrum, *m/z* (I_{rel}, %): 209 $[M]^+$ (5), 196 $[C_{10}H_{14}NO_3]^+$ (5), 166 $[C_9H_{12}NO_2]^+$ (21), 122 $[C_7H_8NO]^+$ (31), 107 $[C_7H_{14}NO)]^+$ (23), 104 $[C_4H_{10}O_2]^+$ (100), 77 $[C_6H_5]^+$ (58).

3-(3-Methoxyphenyl)-1,5,3-dioxazepane (Ie). Yield 67 (*a*), 81% (*b*), mp 122–124°C. ^1H NMR spectrum, δ,

ppm: 3.47–3.82 m (7H, CH_2, CH_3), 4.87 s (4H, CH_2), 6.28–7.15 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 55.14 (C^{15}), 69.40 ($C^{6,7}$), 80.66 ($C^{2,4}$), 102.18 (C^{9}), 105.46 (C^{11}), 108.33 (C^{13}), 129.78 (C^{12}), 147.80 (C^{8}), 158.26 (C^{10}).

3-(4-Methoxyphenyl)-1,5,3-dioxazepane (If). Yield 62% (*a*), 80% (*b*), mp 129–130°C. ^1H NMR spectrum, δ, ppm: 3.43–3.70 m (7H, CH_2, CH_3), 4.87 s (4H, CH_2), 6.40–7.28 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 59.89 (C^{15}), 73.83 ($C^{6,7}$), 81.07 ($C^{2,4}$), 112.66 ($C^{10,12}$), 129.92 ($C^{9,13}$), 146.74 (C^{8}), 160.69 (C^{11}).

3-(2-Nitrophenyl)-1,5,3-dioxazepane (Ig). Yield 64% (*a*), 60% (*b*), mp 140–143°C. ^1H NMR spectrum, δ, ppm: 3.69 m (4H, CH_2), 5.27 s (4H, CH_2), 7.31–7.83 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 68.27 ($C^{6,7}$), 79.30 ($C^{2,4}$), 109.10 (C^{10}), 114.07 (C^{13}), 120.56 (C^{12}), 129.75 (C^{11}), 147.02 (C^{8}), 149.09 (C^{9}). Mass spectrum, *m/z* (I_{rel}, %): 224 $[M]^+$ (60), 195 $[C_9H_{11}N_2O_3]^+$ (50), 151 $[C_7H_7N_2O_2]^+$ (100), 137 $[C_6H_5N_2O_2]^+$ (15), 104 $[C_4H_{10}O_2]^+$ (35), 77 $[C_6H_5]^+$ (23).

3-(3-Nitrophenyl)-1,5,3-dioxazepane (Ih). Yield 69% (*a*), 77% (*b*), mp 133–134°C. ^1H NMR spectrum, δ, ppm: 3.78 m (4H, CH_2), 5.04 s (4H, CH_2), 7.24–7.90 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 69.52 ($C^{6,7}$), 80.16 ($C^{2,4}$), 109.95 (C^{9}), 114.35 (C^{11}), 121.17 (C^{13}), 129.02 (C^{12}), 147.48 (C^{8}), 148.51 (C^{10}).

3-(4-Nitrophenyl)-1,5,3-dioxazepane (Ii). Yield 66% (*a*), 59% (*b*), mp 156–157°C. ^1H NMR spectrum, δ, ppm: 3.54 m (4H, CH_2), 4.97 s (4H, CH_2), 7.38–7.90 m (4H, CH). ^{13}C NMR spectrum, δ, ppm: 71.05 ($C^{6,7}$), 82.62 ($C^{2,4}$), 109.60 ($C^{10,12}$), 128.93 ($C^{9,13}$), 146.98 (C^{8}), 149.20 (C^{9}).

3-(5-Methylisoxazol-3-yl)-1,5,3-dioxazepane (IIa). Yield 60% (*b*). ^1H NMR spectrum, δ, ppm: 2.14 m (3H, CH_3), 3.54 d (4H, CH_2, *J* 4Hz), 5.43 s (4H, CH_2), 7.36 s (1H, CH). ^{13}C NMR spectrum, δ, ppm: 15.13 (C^{13}), 68.25 ($C^{6,7}$), 86.30 ($C^{2,4}$), 89.17 (C^{12}), 140.72 (C^{8}), 165.60 (C^{11}).

3-(5-Methylpyridin-2-yl)-1,5,3-dioxazepane (IIb). Yield 64% (*b*). ^1H NMR spectrum, δ, ppm: 2.18 s (3H, CH_3), 3.22 d (4H, CH_2, *J* 4.4 Hz), 5.35 s (4H, CH_2), 7.16–7.20 m (3H, CH). ^{13}C NMR spectrum, δ, ppm: 20.17 (C^{14}), 71.03 ($C^{6,7}$), 87.15 ($C^{2,4}$), 101.30 (C^{13}), 119.20 (C^{11}), 128.26 (C^{12}), 140.40 (C^{10}), 151.91 (C^{8}).

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