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ORIGINAL PAPER

One-pot synthesis of novel *s*-triazine-containing polyphenols and imidazotriazinium salts

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Abstract Study of the reaction of aminoacetal containing 1,3,5-triazine moiety with phenols is reported. Reaction conditions leading to the formation of either polyphenols modified with 1,3,5-triazine moiety or previously unknown 6-arylimidazo[1,2-*a*][1,3,5]triazin-5-ium salts with good yields are determined. Formation of triazinium salts proceeds via the dearylation of initially formed triazine-containing polyphenols.

Keywords Arenes · Heterocycles · Cyclizations · Resorcinol · Amino aldehyde

Introduction

Condensation of resorcinol with aldehydes and acetals is intensively studied for recent decades [1] and represents a convenient method of synthesis of polyphenol compounds of both polymer [2] and macrocyclic structure [3, 4]. Despite the fact that a broad range of aliphatic and aromatic aldehydes is involved in reaction, until recently, insufficient attention was devoted to the reactions of resorcinol with aldehydes containing functional groups at α-carbon atom [5, 6].

Earlier, within the study of the reaction of resorcinol with α-substituted acetals [7–9], we devised the method of synthesis of polyphenols modified by nitrogen- [10, 11] and phosphorus-containing [12] groups, which enables one to synthesize the target products with high yields.

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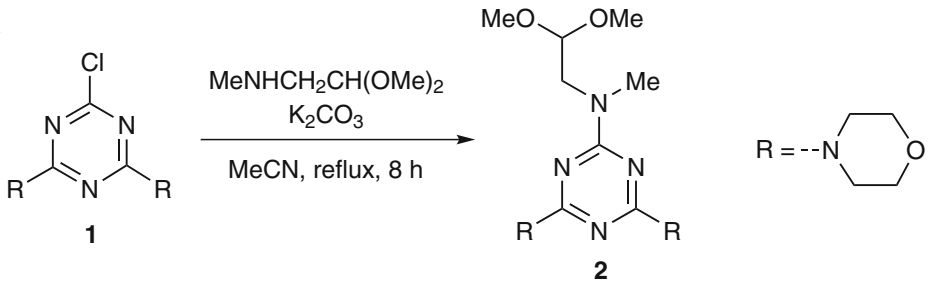
Following the studies in this field, we have pointed our attention to acetals containing 1,3,5-triazine moiety. Derivatives of *sym*-triazine attract careful attention of researchers due to the wide range of biological activity. In particular, it was reported on anti-protozoa [13], antiviral [14], antimicrobial [15–19], antimalarial [20, 21], and anticancer [22] activities of these compounds; their use as modulators of estrogenic receptors [23] and inhibitors of cycline-dependent kinases [24].

Results and discussion

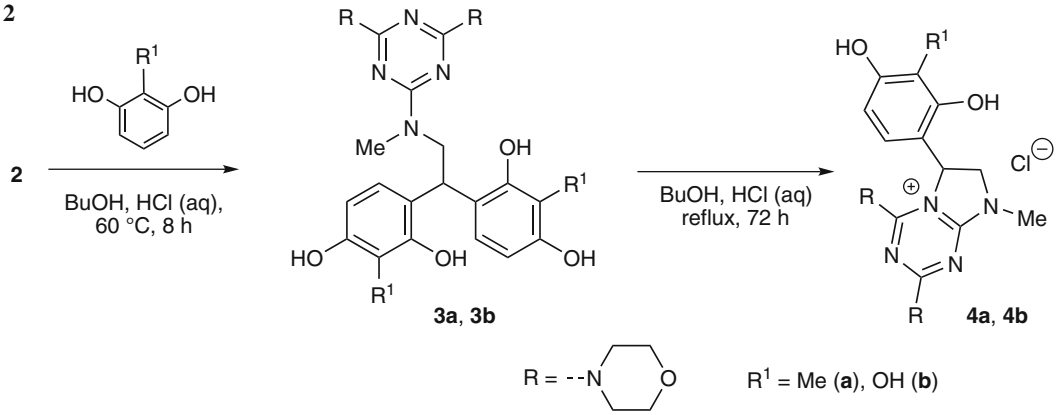
Initial acetal was synthesized from the easily available cyanuric chloride. Its reaction with two equivalents of morpholine with alkali yields 6-chloro-1,3,5-triazine-2,4-diamine (**1**) [25]. Further reaction of this compound with *N*-methylaminoacetaldehyde dimethyl acetal made it possible to synthesize target *N*-(2,2-dimethoxyethyl)-*N*-methyl-4,6-dimorpholino-1,3,5-triazin-2-amine (**2**, Scheme 1).

Reaction of acetal **2** with 2-methylresorcinol in boiling ethanol in the presence of hydrochloric acid gives rise to the formation of the mixture of two main products. Analysis of spectral data made it possible to establish that one of them is the product of condensation of acetal **2** with two molecules of 2-methylresorcinol and has the structure of 4,4'-[2-[(4,6-dimorpholino-1,3,5-triazin-2-yl)(methyl)-amino]ethane-1,1-diyl]bis(2-methylbenzene-1,3-diol) (**3a**). The latter product corresponded to unexpected 6-(2,4-dihydroxy-3-methylphenyl)-8-methyl-2,4-dimorpholino-7,8-dihydro-6*H*-imidazo[1,2-*a*][1, 3, 5]triazin-5-ium chloride (**4a**, Scheme 2). The structure of the compound **4a** was unambiguously confirmed by 2D HSQC and HMBC experiments. In HMBC spectrum, resonance of methyne group proton at 4.23 ppm shows cross-peak to resonance

Scheme 1



Scheme 2



of carbon atom of triazole ring at 153.42 ppm, which proves the imidazole ring formation. Same proton has also the cross-peak with resonance of carbon atom of resorcinol fragment at 156.15 ppm. At the same time, no cross-peaks are observed for the resonances of protons of methylene group and triazine ring carbon atoms. So, the methylene group does not adjoin the triazine ring and obtained data suggests the 6-arylsubstituted heterocycle formation.

There are only several publications describing the synthesis of triazinium salts [26–28] or indicating on the possibility of their formation as unstable intermediates [29, 30]. There are no data on the synthesis of aryl-substituted compounds of this type in published data.

Further study of this reaction showed that decrease in temperature and in time of reaction increases the fraction of product of dimerization in reaction mixture, while increase in temperature and time of reaction provides the formation of triazinium salt. When performing reaction in boiling butanol for 72 h, triazinium salt **4a** was isolated as the only product. Decrease in temperature to 60°C and time of reaction to eight hours made it possible to synthesize polyphenol **3a** with the yield of 60 %.

Long-term boiling of the dimer **3a** obtained in butanol with hydrochloric acid also gives rise to the formation of compound **4a**. Triazinium salt **4a** remains unchanged at boiling under the same conditions; this proves the absence of equilibrium between two products. Thus, it can be suggested that polyphenol **3a** is the product of kinetic control of reaction, while triazinium salt **4a** represents the product of thermodynamic control.

Reaction of acetal **2** with pyrogallol proceeds according to analogous scheme. However, it should be noted that, in this case, reaction results in the formation of hardly separable mixture of compounds **3b** and **4b** even under relatively mild conditions and we did not succeed in isolating individual polyphenol **3b**.

Assuming the data obtained, we suggested the following scheme of reaction (Scheme 2). On the first step, reaction of acetal **2** with phenol takes place with the formation of polyphenol **3**, dearylation of which at elevated temperature gives triazinium salt **4** as product. It should be noted that there are no analogous transformations in published data.

Thus, as a result of the studies performed, we devised a convenient single-step method of synthesis of polyphenols containing 1,3,5-triazine fragment, as well as novel aryl-substituted imidazotriazinium salts according to the reaction of triazine-containing acetals with polyatomic phenols. It was established that the formation of triazinium salts proceeds according to dearylation and subsequent intramolecular heterocyclization of polyphenols.

Experimental

Commercially available compounds were used without further purification. Solvents were purified according to standard procedures. The NMR spectra were recorded on an Avance 600 instrument with the working frequency of 600.13 MHz for ^{1}H and 150.90 MHz for ^{13}C. Signals of residual protons of solvent in ^{1}H NMR spectra were used as references for the measurements of chemical shift. IR spectra were recorded on a Vector 22 (Bruker) spectrometer. Results of elemental analyses (C, H, N, Cl) were found to be in good agreement (± 0.3 %) with the calculated values. 2-Chloro-4,6-dimorpholino-1,3,5-triazine (**1**) was prepared according to known procedure, m.p. 173°C (Ref. [25] 173–174°C).

N-(2,2-Dimethoxyethyl)-N-methyl-4,6-dimorpholino-1,3,5-triazin-2-amine (**2**, $C_{16}H_{28}N_6O_4$)

To the solution of 5.00 g (17.48 mmol) 2-chloro-4,6-dimorpholino-1,3,5-triazine (**1**) and 2.08 g (17.48 mmol) *N*-methylaminoacetaldehyde dimethyl acetal in 70 cm^3 acetonitrile, 5 g potassium carbonate was added. Reaction mixture was refluxed for 8 h, filtered, and evaporated in vacuo to give 5.60 g (87.5 %) **2**. M.p.: 140°C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.12$ (s, 3H, CH_3-N), 3.38 (s, 6H, CH_3-O), 3.62 (d, $J = 5.37$ Hz, 2H, CH_2), 3.66-3.70 (m, 8H, morpholine), 3.73 (m, 8H, morpholine), 4.56 (t, $J = 5.00$ Hz, 1H, CH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 36.82$ (CH_3-N), 43.67 (CH_2-N, morpholine), 50.65 (CH_2), 54.28 (CH_3-O), 66.61 (CH_2-O, morpholine), 103.46 (CH), 164.51, 165.26, 165.56 ($C_{triazine}$) ppm.

4,4'-[2-[(4,6-Dimorpholino-1,3,5-triazin-2-yl)(methyl)amino]-ethane-1,1-diyl]bis(2-methylbenzene-1,3-diol) (**3a**, $C_{28}H_{36}N_6O_6$)

To the solution of 1.50 g (4.07 mmol) *N*-(2,2-dimethoxyethyl)-*N*-methyl-4,6-dimorpholino-1,3,5-triazin-2-amine (**2**) and 1.00 g (8.06 mmol) 2-methylresorcinol in 20 cm^3 1-butanol 2 cm^3 concentrated hydrochloric acid was added at room temperature. Reaction mixture was heated at 60°C for 8 h, cooled, and transferred to 200 cm^3 diethyl ether. Precipitate formed was filtered off, washed multiple times with chloroform, and dried in vacuum (0.01 torr, 40 °C, 2 h) to give 1.28 g (60 %) **3a**. M.p.: 193–194°C; ^{1}H NMR (600 MHz, CD_3OD): $\delta = 2.05$ (s, 6H, CH_3-C_{aryl}), 3.12 (s, 3H, CH_3-N), 3.74 (m, 16H, morpholine), 4.24 (d, $J = 7.57$ Hz, 2H, CH_2), 5.04 (t, $J = 7.93$ Hz, 1H, CH), 6.33 (d, $J = 8.30$ Hz, 2H, CH_{aryl}), 6.92 (d, $J = 8.30$ Hz, 2H, CH_{aryl}) ppm; ^{13}C NMR (150 MHz, CD_3OD): $\delta = 7.67$ (CH_3-C_{aryl}), 35.62 (CH_3-N), 44.87, 45.28 (CH_2-N, morpholine), 53.73 (CH_2-N), 65.98 (CH_2-O), 106.84 (CH_{aryl}), 111.67 (C_{aryl}-CH_3), 120.28 (C_{aryl}-CH), 125.10 (CH_{aryl}), 152.91 (C_{aryl}-OH), 154.34, 154.49 ($C_{triazine}$-N) ppm; IR: $\bar{\nu} = 1{,}609$, 3,271 cm^{-1}; MALDI TOF: *m/z* calcd for $C_{28}H_{36}N_6O_6$ (M^+) 552.26, found 552.27.

6-(2,4-Dihydroxy-3-methylphenyl)-8-methyl-2,4-dimorpholino-7,8-dihydro-6H-imidazo[1,2-a][1, 3, 5]-triazin-5-ium chloride (**4a**, $C_{21}H_{29}ClN_6O_4$)

To the solution of 1.30 g (3.53 mmol) *N*-(2,2-dimethoxyethyl)-*N*-methyl-4,6-dimorpholino-1,3,5-triazin-2-amine (**2**) and 0.83 g (6.69 mmol) 2-methylresorcinol in 20 cm^3 1-butanol 1.5 cm^3 concentrated hydrochloric acid was added at room temperature. Reaction mixture was refluxed for 72 h, cooled, and transferred to 200 cm^3 diethyl ether. Precipitate formed was filtered off, washed multiple times with diethyl ether, and dried in vacuum (0.01 torr, 40 °C, 2 h) to give 1.18 g (72 %) **4a**. M.p.: 199–200°C; ^{1}H NMR (600 MHz, CD_3OD): $\delta = 2.05$ (s, 3H, CH_3-C_{aryl}), 3.15 (s, 3H, CH_3-N), 3.22-3.24 (m, 4H, morpholine), 3.87-3.90 (m, 4H, morpholine), 3.77 (m, 8H, morpholine), 4.23 (t, $J = 10.67$ Hz, 1H, CH), 3.70 (dd, $J = 10.39$ Hz, 5.39 Hz, 1H, CH_2), 5.50 (dd, $J = 10.79$ Hz, 4.92 Hz, 1H, CH_2), 6.35 (d, $J = 8.25$ Hz, 1H, CH_{aryl}), 6.88 (d, $J = 8.33$ Hz, 1H, CH_{aryl}) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): $\delta = 8.89$ (CH_3-C_{aryl}), 30.73 (CH_3-N), 42.50, 45.16 (CH_2-N, morpholine), 53.91, 54.93 (CH_2), 63.08, 65.36 (CH_2-O, morpholine), 79.17 (CH), 106.49 (CH_{aryl}), 109.45 (C_{aryl}-CH_3), 112.09 (C_{aryl}-CH), 116.37 (CH_{aryl}), 146.81, 153.42 ($C_{triazine}$), 154.43 ($C_{triazine}$-N^+), 156.15, 156.34 (C_{aryl}-OH) ppm; IR: $\bar{\nu} = 1{,}605$, 1,672, 1,753, 3,181 cm^{-1}; MALDI TOF: *m/z* calcd for $C_{21}H_{29}ClN_6O_4$ (M^+-Cl) 429.22, found 429.22.

8-Methyl-2,4-dimorpholino-6-(2,3,4-trihydroxyphenyl)-7,8-dihydro-6H-imidazo[1,2-a][1, 3, 5]triazin-5-ium chloride (**4b**, $C_{20}H_{27}ClN_6O_5$)

To the solution of 0.50 g (1.36 mmol) *N*-(2,2-dimethoxyethyl)-*N*-methyl-4,6-dimorpholino-1,3,5-triazin-2-amine (**2**) and 0.34 g (2.70 mmol) pyrogallol in 10 cm^3 1-butanol 1.0 cm^3 concentrated hydrochloric acid was added at room temperature. Reaction mixture was refluxed for 72 h, cooled, and transferred to 200 cm^3 diethyl ether. Precipitate formed was filtered off, washed multiple times with diethyl ether, and dried in vacuum (0.01 torr, 40 °C, 2 h) to give 0.3 g (47 %) **4b**. M.p.: 112–113°C; ^{1}H NMR (600 MHz, CD_3OD): $\delta = 3.15$ (s, 3H, CH_3-N), 3.22-3.30 (m, 4H, morpholine), 3.87–3.90 (m, 4H, morpholine), 3.75–3.79 (m, 8H, morpholine), 4.24 (t, $J = 10.62$ Hz, 1H, CH), 3.72 (dd, $J = 10.50$ Hz, 4.88 Hz, 1H, CH_2), 5.47 (dd, $J = 10.74$, 5.47 Hz, 1H, CH_2), 6.32 (d, $J = 8.30$ Hz, 1H, CH_{aryl}), 6.57 (d, $J = 8.30$ Hz, 1H, CH_{aryl}) ppm; ^{13}C NMR (150 MHz, CD_3OD): $\delta = 28.55$ (CH_3-N), 41.79, 44.80 (CH_2-N, morpholine), 53.17, 53.97 (CH_2), 62.00, 64.06 (CH_2-O, morpholine), 76.58 (CH), 104.99 (CH_{aryl}), 113.83 (C_{aryl}-CH), 117.87 (CH_{aryl}), 142.97, 144.51, 147.12, 152.90 ($C_{triazine}$), 154.45 ($C_{triazine}$-N^+), 155.08 (C_{aryl}-OH)

ppm; IR: $\bar{\nu}$ = 1,604, 1,673, 1,753, 3,173 cm^{-1}; MALDI TOF: *m/z* calcd for $C_{20}H_{27}ClN_6O_5$ (M^+) 466.17, found 466.17.

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