THE FIRST CASE OF DIRECT COUPLING OF HETEROCYCLES WITH CALIXARENES. REACTION OF RESORCINARENES WITH 1,2,4-TRIAZIN-5(*2H*)-ONES

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Dedicated to Professor G. Tolstikov on the occasion of his 70th birthday

Abstract. A convenient method for an one-step coupling of resorcinarenes with 3-R-1,2,4-triazin-5(*2H*)-ones, involving nucleophilic addition to the unsubstituted carbon atom C-6 of triazine ring, has been worked out.

Introduction

Calix[4]arenes are a special class of aromatic macrocycles, which are widely used for creation of pre-organizational receptors. Vase-shaped resorcinarenes and their derivatives are of the interest due to their ability to accommodate both neutral molecules and metal ions. *C*- and *O*-Functionalization of *upper rim* of resorcinarenes increases the molecular cavity and complexation ability. Modification of resorcinarenes by heterocycles is of special interest in this field. Unfortunately up to date such heterocyclic functionalization is not developed enough.

Functionalization of the hydroxy-groups in resorcinarenes is well known (1). Only a few cases of the C-C bond formation by functionalization of resorcinarenes have been reported (2). To our knowledge introduction of heterocyclic moieties to resorcinarenes accompanying with cleavage of =C-H bond of resorcinearene is not described in the literature.

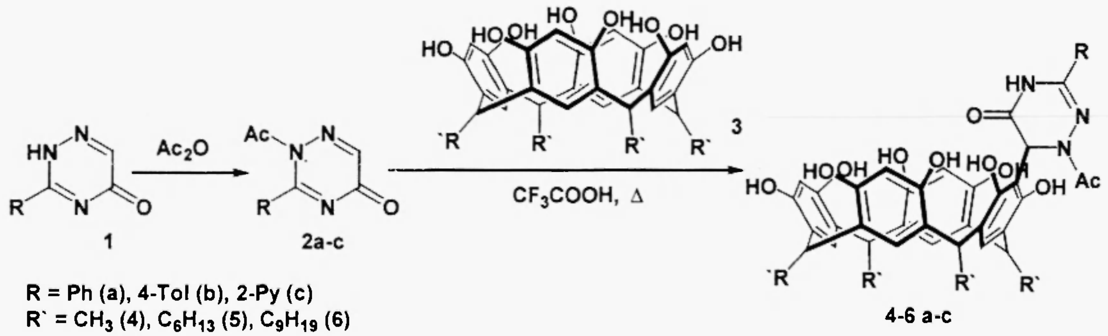
During the last decade the A_N and S_N^H methodologies based on the direct nucleophilic attack at an unsubstituted carbon atom of π-deficient arenes and hetarenes have been developed considerably (3, 4). Using such methods it is possible to carry out one-stage coupling of arylamines, π-excessive hetarenes, phenols and their ethers with different azines without preliminary introduction of nucleofugal groups such as Cl, OR, SO_2R etc. in the hetarene ring. By the methodology described for one-step interaction of resorcinarenes with heterocycles, it is possible to use a minimum of reagents in this reaction, resulting in a decrease of undesirable complex formation and increase of yield and purity of product.

This work presents our first results of functionalization of resorcinarenes aromatic rings by direct carbon-carbon coupling with π-deficient compounds such as 1,2,4-triazin-5(*2H*)-ones.

Results and discussion

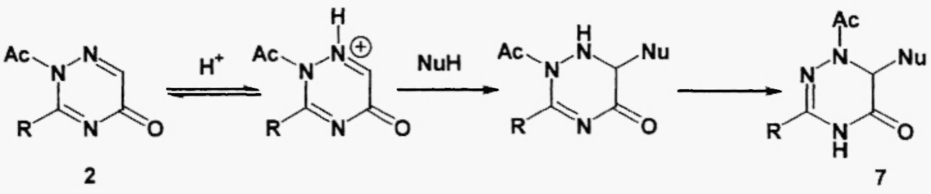
Previously, we showed that the interaction of 1,2,4-triazin-5(2H)-ones **1** with aromatic C-nucleophiles in a mixture of trifluoroacetic acid and acetic anhydride resulted in the formation of stable products of nucleophilic addition to the unsubstituted C-6-atom of the 1,2,4-triazine ring (5, 6). This reaction is accompanied by acylation of the nitrogen atom adjacent to the reaction center. The presence of acylating agent is necessary for this process, otherwise there are formed protolytic unstable adducts which dissociate into starting reagents during workup. Moreover, acylation of triazine ring activates the system for nucleophilic attack. This methodology has been developed in several studies using nucleophiles, such as phenols and their ethers, arylamines, π-excess heterocycles, and so on (5-8) .

In the present investigation we have tried to extend the one-step coupling of heterocycles with aromatic C-nucleophiles for functionalization of *upper rim* of resorcinarenes with 1,2,4-triazine fragments. It has been established that resorcinarenes are heterylated on the *upper rim* by 1,2,4-triazin-5-ones under the acid conditions and in the presence of organic anhydrides. Introduction of acid anhydride to the reaction results in the formation of difficulty separated mixture of products with different degree of acylation of oxy-groups. This can be avoided by using 2-acetyl-1,2,4-triazinones **2 a-c** in the reaction. The interaction of **2 a-c** with resorcinarenes results in the formation of 1:1 addition products **4-6 a-c** without formation of any by-products (Scheme 1).



Scheme 1

It should be noted that the reaction takes place only in the presence of trifluoroacetic acid. The electrophilic unit reacting with resorcinarene is the protonated 2-acyl-3-R-1,2,4-triazin-5-one. In the course of the reaction the acylotropic rearrangement into the more preferred N1-acyl isomer 7 takes place (Scheme 2).



Scheme 2

Structural elucidation of the obtained compounds was made by means of ^{1}H-NMR. The addition product formation was proved by appearance of the signal of the proton at sp^3-hybridizated carbon in triazine cycle in the region of δ 5.90-6.14 ppm. Introduction of the heterocycle in calixarene affords confusing of the initial *vase*-conformation. The ^{1}H NMR spectra (DMSO-d_6, aceton-d_6) of compounds **6,7 a-c** show an upfield shift for the upper rim aromatic protons of 0.5-1.2 ppm. Moreover, introduction of 1,2,4-triazine units to resorcinarenes results in the appearance of magnetically nonequivalence of three *upper rim* and four *lower rim* aromatic protons. ^{1}H-NMR spectra show that the signals of these protons are multiplets at the regions of δ 6.14-6.27 (*upper rim*) and δ 7.09-7.25 (*lower rim*) ppm.

In conclusion it should be noted that the described reaction is the first example of the direct one-step C-C coupling of calixarenes with heterocycles.

Experimental

Flash chromatography was performed on Kieselgel Woelm DC silica gel. All melting points are uncorrected and were measured on a Boetius melting point apparatus. Elemental analyses were performed on Carlo Erba 1108 CHNO Analyzer. The ^{1}H-NMR spectra were recorded on a Bruker DRX 400 (400MHz) spectrometer with TMS as an internal standard. All signals are given in ppm. Mass-spectra were obtained on a Maldi TOF Dinamo Finnizar with 1,8,9-trihedroxyanthracene and para-nitro-aniline as a die.

General procedure for preparation of 2-acyl-3-R-1,2,4-triazin-5-one (2 a-c).

3-R-1,2,4-triazin-5(2H)-one (1.7 mmol) was dissolved by heating in 1.5 ml of acetic anhydride. The reaction mixture was cooled and the precipitate was filtered off to give 2-acyl-3-R-1,2,4-triazin-5(2H)-one. **2a**: yield 85 %, mp 140-141^{0}C. Anal. calcd. for $C_{11}H_9N_3O_2$: C, 61.40; H, 4.20; N, 19.53. Found: C, 61.66; H, 3.98; N, 19.88. **2b**: yield 92 %. Anal.calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.12; H, 4.62; N, 18.16. **2c**: yield 78 %. Anal.calcd. for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.71; N, 25.92. Found: C, 55.68; H, 4.01; N, 26.14.

General procedure for preparation of 18-(1-acetyl-3-R-5-oxy-1,2,4-triazin-6-yl)-1,21,23,25-tetraalkylresorcinarene 4 b-c, 5 a-c, 6c.

2-Acyl-3-R-1,2,4-triazin-5-one (0.6 mmol) and resorcinarene (0.6 mmol) were dissolved in the mixture of 2 ml of trifluoracetic acid and 4 ml of chloroform. The reaction mixture was refluxed for 4-6 h. The solvent was removed *in vacuo*. The oil residue was subjected to flash chromatography yielding 1:1 product of hetarylation of resorcinarene. **4b**: yield 33%, mp 227 ^{0}C (decomp). δ_H (DMSO-d_6): 11.23 (1H, br.s., NH), 6.12 (1H, s, C^6-H), 7.09-7.79 (9H, m, Ar, Tol), 6.14-6.27 (2H, m, Ar), 4.40-4.42 (4H, m, CH), 1.54-2.37 (18H, m, CH_3(Tol), CH_3, Ac). Anal.calcd. for $C_{44}H_{43}N_3O_{10}$: C, 68.29; H, 5.60; N, 5.43. Found: C, 68.42; H, 5.89; N, 5.21. **4c**: yield 48%, mp 195-198 ^{0}C. δ_H (DMSO-d_6): 8.65-8.66 (1H, m, Py), 8.17-8.21 (1H, m, Py), 7.92-7.96 (1H, m, Py), 7.08-7.54 (6H, m, Py, Ar), 5.95-6.24 (3H, m, Ar, C^6-H), 4.29-4.51 (4H, m, CH), 1.53-1.76 (12H, m, CH_3), 2.31-2.36 (3H, m, Ac). Anal.calcd. for $C_{42}H_{40}N_4O_{10}$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.43; H, 5.48; N, 7.23. **5a:** yield 44%, mp > 250 ^{0}C . δ_H (Acetone-d_6): 8.49-8.63 (2H, m, Ph), 8.02-8.24 (3H, m, Ph), 7.38-7.81 (4H, m, Ar), 6.35 (1H, s, C^6-H), 6.00-6.34 (3H, m, Ar), 4.32-4.55 (4H, m, CH), 2.40-2.42 (3H, m, Ac), 2.11-2.20 (8H, m, CH_2), 1.25-1.54 (32H, m, CH_2), 0.98-1.08 (12H, m, CH_3). Anal. calcd. for $C_{63}H_{81}N_3O_{10}$: C, 72.73; H, 7.85; N, 4.04. Found: C, 72.41; H, 7.93; N, 3.95.m/z: 783.79 ([M^+] + [Na^+]), 799.89 ([M^+] + [K^+]). **5b:** yield 42%, mp 220 ^{0}C (decomp). δ_H (DMSO-d_6): 11.24 (1H, br.s, NH), 6.15 (1H, s, C^6-H), 7.15-7.27 (9H, m, Ar, Tol), 7.79-7.91 (2H, m, Ar), 4.14-4.50 (4H, m, CH), 2.39-2.41 (3H, m, Ac), 2.01-2.35 (8H, m, CH_2) 2.09-2.48 (3H, m, CH_3(Tol)), 1.24-1.53 (32H, m, CH_2), 1.01 (12H, m, CH_3). Anal.calc. for $C_{64}H_{83}N_3O_{10}$: C, 72.91; H, 7.93; N, 3.99. Found: C, 72.84; H, 7.87; N, 3.92. **5c:** yield 53%, mp 195-198 ^{0}C. δ_H (Acetone-d_6): 8.63-8.66 (1H, m, Py), 7.94-8.17 (1H, m, Py), 7.52-7.56 (1H, m, Py), 7.10-7.13 (6H, m, Py, Ar), 5.98-6.15(3H, m, Ar, C^6-H), 4.13-4.17 (4H, m, CH), 2.49-2.52 (3H, m, Ac), 2.39-2.45 (8H, m, CH_2), 1.33-1.41 (32H, m, CH_2), 0.87-1.01 (12H, m, CH_3,). Anal. calcd. for $C_{62}H_{80}N_4O_{10}$: C, 71.51; H, 7.74; N, 5.38. Found: C, 71.36; H, 7.82; N, 5.15. **6c:** yield 62%, mp 238 ^{0}C (decomp). δ_H (DMSO-d_6): 8.65-8.67 (1H, m, Py), 8.15-8.17 (1H, m, Py), 7.96-7.97 (1H, m, Py), 7.52-7.58 (1H, m, Py), 7.35 (4H, br.s, Ar (*lower rim*)), 6.17-6.25 (3H, m, Ar), 6.14 (1H, s, C^6-H), 4.27-4.32 (4H, m, CH), 2.24-2.29 (3H, m, Ac), 0.86-0.97 (12H, m, CH_3), 1.28-1.37 (56H, m, CH_2), 2.08-2.31 (8H, m, CH_2). Anal. calcd. for $C_{74}H_{103}N_4O_{10}$: C, 73.54; H, 8.58; N, 4.63. Found: C, 73.52; H, 8.41; N, 4.42.

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References

1. W. Sliwa, G. Matusiak, M. Deska, Heterocycles. **57**, 2179 (2002).
2. J. Vicent and V. Böhmer, A Versatile Class of Macrocyclic Compounds in Z. Asfari (Ed.) Calixarenes. Kluwer Academic Publishers, Dordrecht, Boston, London, 1991
3. O.N. Chupakhin, V.N. Charushin, H.C. van der Plas, Nucleophilic Atomatic Substitution of Hydrogen, Academic Press, N.Y., San Diego, 1994.
4. V.N. Charushin, O.N. Chupakhin, H.C. van der Plas, Adv. Het.Chem. **43**, 301 (1988)
5. O.N. Chupakhin, D.G. Beresnev, G.L. Rusinov, H. Neunhoeffer. J. Heterocycl.Chem. **34**, 573 (1997)
6. G.L. Rusinov, D.G. Beresnev, N.A. Itsikson, O.N. Chupakhin, Heterocycles. **55**, 2349 (2001)
7. D.G. Beresnev, G.L. Rusinov, V.L. Rusinov, O.N. Chupakhin, Russ.J.Org.Chem. **34,** 452 (1998)
8. G.L. Rusinov, D.G. Beresnev, O.N. Chupakhin, Russ.J.Org.Chem. **34,** 423 (1998)

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