ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 7, pp. 1287–1292. © Pleiades Publishing, Ltd., 2014.
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Synthesis of Functionally Substituted 2,2'-Arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones)

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Received January 23, 2014

Abstract—Condensation of functionally substituted benzaldehydes and isoxazolyl-3-carbaldehyde with dimedone in the presence of catalytic amounts of triethylamine in methanol afforded functionally substituted 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones).

Keywords: isoxazolyl-3-carbaldehyde, dimedone, carboranes, xanthenes, BNCT agents

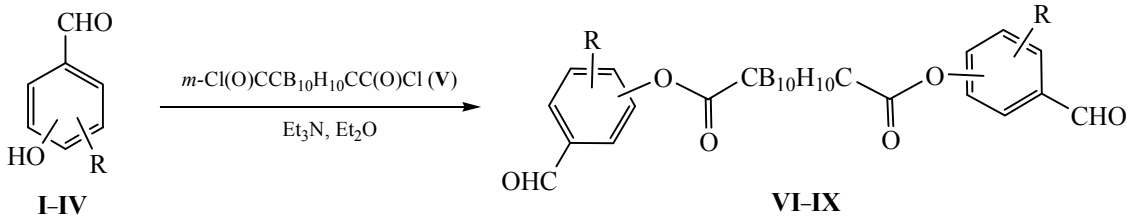
DOI: 10.1134/S1070363214070068

Several functionally substituted benzaldehydes derivatives possess high biological activity that stimulates development of studies on their synthesis and chemical modifications [1–4]. Substituted aromatic benzaldehydes **VI**–**IX**, **XI**–**XVI**, **XXXI**, **XXXIII**, **XXXIV** and isoxazolyl-3-carbaldehydes **XXIII**, **XXIV** containing fragments of halo- and nitroaromatic derivatives, carborane cluster compounds, or azole heterocycles are of some interest for their bioassay to search for new insecticides and drugs, agents of boron neutron capture therapy of cancer (BNCT) (Schemes 1–7).

In this work we developed preparative method for the synthesis of functionally substituted 2,2'-arylmehylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones) **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**, **XXXVI** via Knoevenagel condensation of benzaldehydes **VI**–**IX**, **XI**–**XVI**, **XXXI**, **XXXIII**, **XXXIV** and isoxazol-3-carbaldehydes **XXIII**, **XXIV** with dimedone **X** in methanol in the presence of catalytic amounts of triethylamine [5, 6]. Yields of **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**, **XXXVI** were 75–88%. This method is a general-purpose procedure of preparation of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones), because it excludes completely the hydrolysis or alcoholysis of the labile ester groups and provides the target compounds in high yields.

Functionally substituted diesters of *m*-carboranedicarboxylic acids **VI**–**IX**, vanillin and vanillal diesters **XI**–**XVI**, **XXXIII**, **XXXIV** [1], 1,1'-biphenyl-4,4'-dicarbaldehyde **XXXI**, and isoxazol-3-carbaldehydes **XXIII**, **XXIV** [7] were used as the starting aldehydes. Compounds **VI**–**IX** were obtained by esterification of

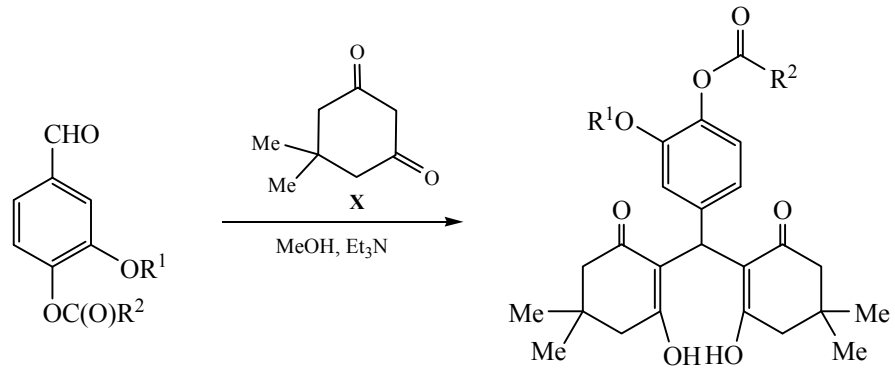
Scheme 1.



I–**IV** **VI**–**IX**

R = H, 4-HO or –C(O)O– (**I**, **VI**); R = 4-MeO, 3-HO or –C(O)O– (**II**, **VII**); R = 3-MeO, 4-HO or –C(O)O– (**III**, **VIII**); R = 3-EtO, 4-HO or –C(O)O– (**IV**, **IX**).

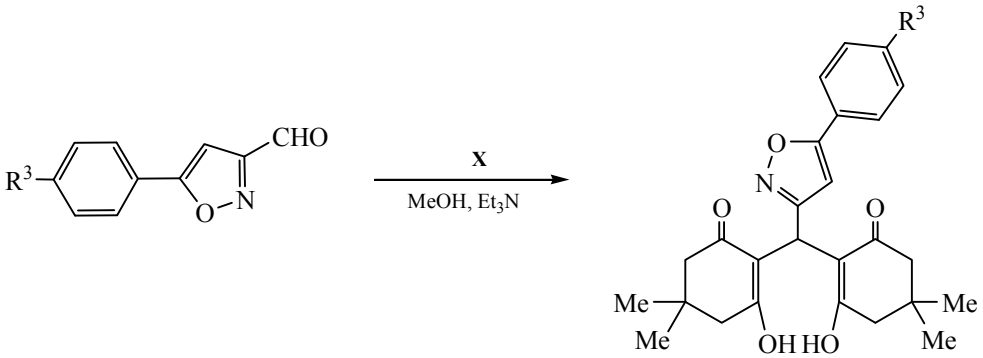
Scheme 2.



XI–XVI **XVII–XXII**

R^1 = Me, R^2 = 2,4-$Cl_2C_6H_3$ (**XI**, **XVII**), *m*-$HCB_{10}H_{10}C$– (**XII**, **XVIII**); R^1 = Et, R^2 = 4-MeC_6H_4 (**XIII**, **XIX**), 2,4-$Cl_2C_6H_3$ (**XIV**, **XX**), 4-$O_2NC_6H_4$ (**XV**, **XXI**), *m*-$HCB_{10}H_{10}C$– (**XVI**, **XXII**).

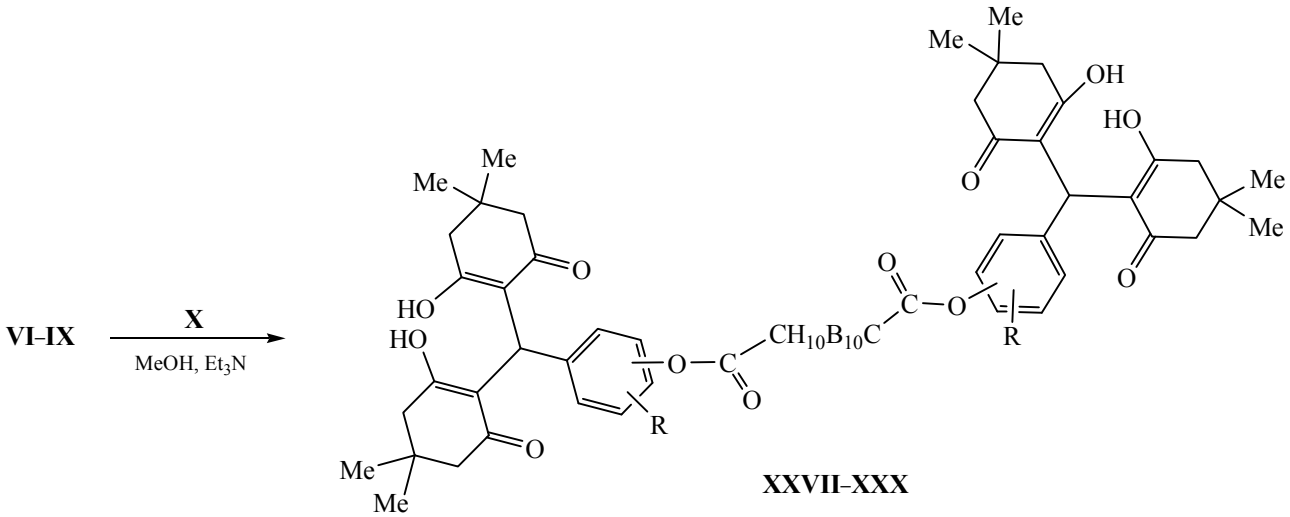
Scheme 3.



XXIII, XXIV **XXV, XXVI**

R^3 = H (**XXIII**, **XXV**), Me (**XXIV**, **XXVI**).

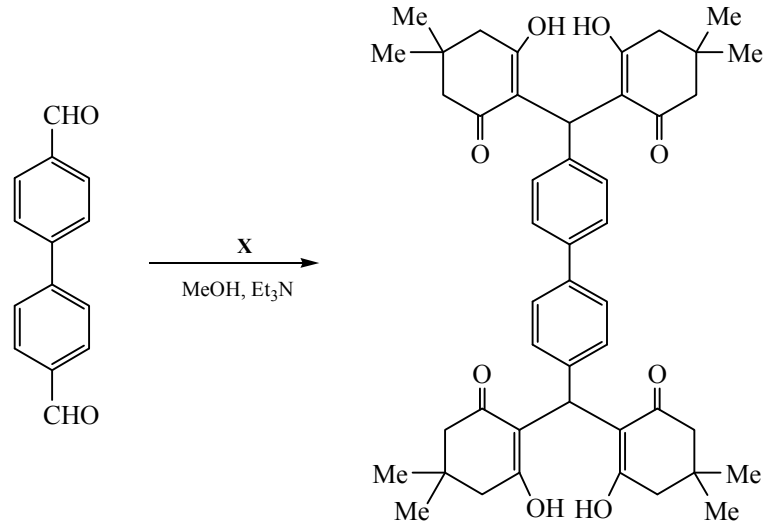
Scheme 4.



XXVII–XXX

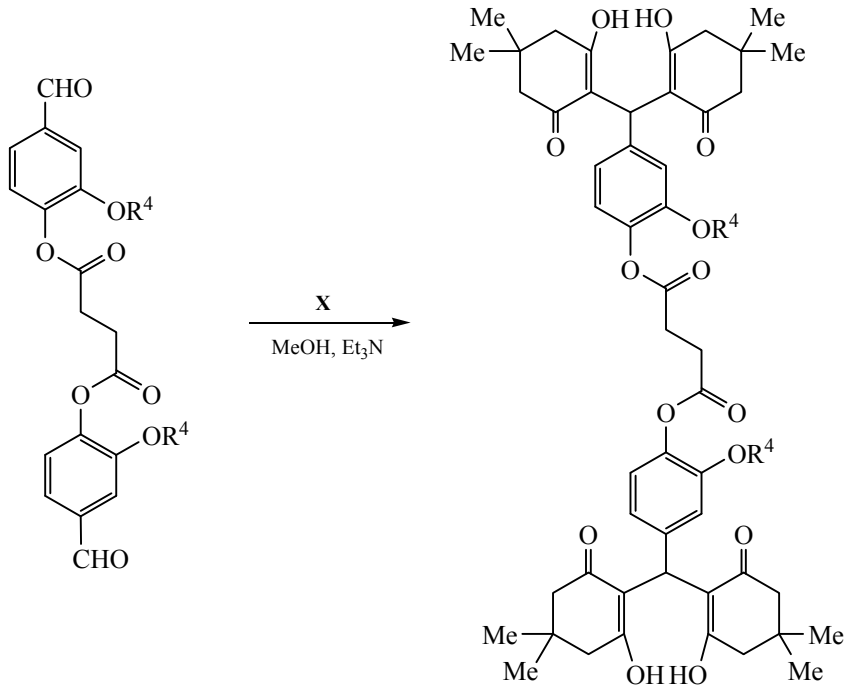
R = H, 4-C(O)O– (**VI**, **XXVII**); R = 4-MeO, 3-C(O)O– (**VII**, **XXVIII**); R = 3-MeO, 4-C(O)O– (**VIII**, **XXIX**); R = 3-EtO, 4-C(O)O– (**IX**, **XXX**).

Scheme 5.



XXXI **XXXII**

Scheme 6.



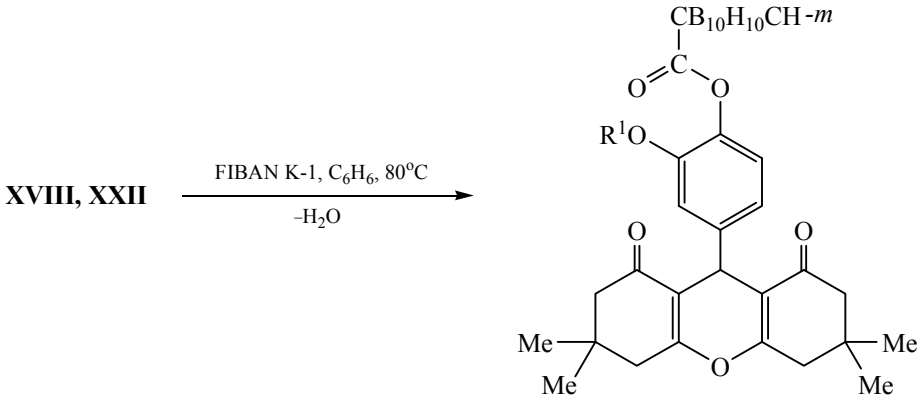
XXXIII, XXXIV **XXXV, XXXVI**

hydroxybenzaldehydes **I**–**IV** with *m*-carboranedicarboxylic acid dichloride **V** in the presence of triethylamine (Scheme 1).

We performed cyclization of *m*-carborane compounds **XVIII**, **XXII** in benzene in the presence of sulfocationite FIBAN K-1 as the catalyst [8, 9] with distilling off the liberated water using a Dean–Stark trap (Scheme 2). The corresponding *m*-carborane-containing 3,3,6,6-trimethyl-9-aryl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-diones **XXXVII**, **XXXVIII** were obtained in a yield of 76 and 79%, respectively (Scheme 7).

In order to prevent hydrolysis or alcoholysis of the ester groups in the starting and target compounds **VI**–

Scheme 7.



R^1 = Me (**XVIII**, **XXXVII**), Et (**XXII**, **XXXVIII**).

IX, **XI**–**XXII**, **XXVII**–**XXX**, **XXXIII**–**XXXVI**, **XXXVII**, **XXXVIII** we selected optimal reaction conditions. The obtained functionally substituted 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones) **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**, **XXXVI** and xanthenes **XXXVII**, **XXXVIII** were colorless crystalline substances. Their composition and structure were confirmed by elemental analysis, IR, ^{1}H

Yields, melting points, and elemental analysis data of **VI**, **VII**, **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**–**XXXVIII**

Comp. no.	Yield, %	mp, °C	Found, %				*M*	Calculated, %				$[M]^+$ $[M-H_2O]^+$ $[M-2H_2O]^+$	*M*
			C	H	B (Cl)	N		C	H	B (Cl)	N		
VI	87	99–100	49.66	4.67	24.07	–	$C_{18}H_{20}B_{10}O_6$	49.08	4.58	24.54	–	440	440.46
VII	94	186–187	48.25	4.94	21.20	–	$C_{20}H_{24}B_{10}O_8$	47.99	4.83	21.60	–	500	500.51
XVII	80	177–178	63.72	5.68	11.75	–	$C_{31}H_{32}Cl_2O_7$	63.38	5.49	12.07	–	568	587.49
XVIII	88	218–219	55.89	7.13	18.11	–	$C_{27}H_{40}B_{10}O_7$	55.46	6.90	18.49	–	566	584.71
XIX	75	82–83	72.88	7.19	–	–	$C_{33}H_{38}O_7$	72.51	7.01	–	–	528	546.65
XX	82	101–102	64.25	5.86	11.49	–	$C_{32}H_{34}Cl_2O_7$	63.90	5.70	11.79	–	582	601.51
XXI	77	156–157	66.83	5.90	–	2.14	$C_{32}H_{35}NO_9$	66.54	6.11	–	2.42	559	577.62
XXII	83	178–179	56.76	7.22	17.68	–	$C_{28}H_{42}B_{10}O_7$	56.17	7.07	18.06	–	580	598.74
XXV	78	191–192	71.95	6.78	–	2.98	$C_{26}H_{29}NO_5$	71.70	6.71	–	3.22	417	435.51
XXVI	80	200–201	72.38	7.20	–	2.90	$C_{27}H_{31}NO_5$	72.14	6.95	–	3.12	431	449.54
XXVII	87	129–130	62.50	6.84	10.92	–	$C_{50}H_{64}B_{10}O_{12}$	62.22	6.68	11.20	–	929	965.15
XXVIII	85	153–154	61.22	6.60	10.34	–	$C_{52}H_{68}B_{10}O_{14}$	60.92	6.69	10.55	–	989	1025.20
XXIX	84	238–239	61.30	6.87	10.18	–	$C_{52}H_{68}B_{10}O_{14}$	60.92	6.69	10.55	–	989	1025.20
XXX	81	224–225	61.99	6.95	9.87	–	$C_{54}H_{72}B_{10}O_{14}$	61.58	6.89	10.26	–	1016	1053.25
XXXII	75	245–246	75.61	7.18	–	–	$C_{46}H_{54}O_8$	75.18	7.41	–	–	698	734.92
XXXV	81	244–245	68.86	7.00	–	–	$C_{52}H_{62}O_{14}$	68.55	6.86	–	–	874	911.04
XXXVI	82	202–203	69.39	7.02	–	–	$C_{54}H_{66}O_{14}$	69.06	7.08	–	–	902	939.09
XXXVII	76	245–246	57.38	6.77	18.91	–	$C_{27}H_{38}B_{10}O_6$	57.22	6.76	19.08	–	566	566.70
XXXVIII	79	205–206	58.20	7.04	18.35	–	$C_{28}H_{40}B_{10}O_6$	57.91	6.94	18.62	–	580	580.72

NMR spectroscopy and chromato-mass-spectrometry data (see table).

In the IR spectra of 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones) **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**, **XXXVI** characteristic absorption bands were observed of CH_{Ar} (3081, 3059, 3023, 776, 721, 695 cm^{-1}), CH_{aliph} (2962, 2930, 2872 cm^{-1}), $C{=}O_{ester}$ (1765–1720 cm^{-1}), C=C–C=O and $C{=}C_{Ar}$ (1595, 1510 and 1375 cm^{-1}), C–O (1275–1010 cm^{-1}) and no absorption band of C=O of the starting aldehydes at 1695–1680 cm^{-1} [1, 7]. The IR spectra of xanthenes **XXXVII**, **XXXVIII** contain characteristic absorption bands of CH_{carb} (3054 cm^{-1}), CH_{Ar} (3070, 3059, 3004, 842, 820, 760, 684, 570 cm^{-1}), CH_{aliph} (2958, 2946, 2835, 2873, 2830 cm^{-1}), $C{=}O_{ester}$ (1760–1758 cm^{-1}), C=C–C=O and $C{=}C_{Ar}$ (1680, 1666, 1626, 1606, 1508, 1376 cm^{-1}) and C–O (1360, 1277, 1252, 1195, 1165, 1123, 1032, 995 cm^{-1}).

In the ^1H and ^{13}C NMR spectra of **VI**, **VII**, **XVII**–**XXII**, **XXV**–**XXX**, **XXXII**, **XXXV**, **XXXVI**, **XXXVII**, **XXXVIII** there are signals of all the structural fragments (aromatic, carborane, isoxazole, ester group) [1, 7].

The synthesized compounds contain pharmacophore fragments. They will be screened for the biological activity to establish a link between their structure and pharmacological activity and to create new drugs [10–13] and agents for boron neutron capture therapy of cancer [14, 15].

EXPERIMENTAL

IR spectra were recorded on a Nicolet Protégé-460 FTIR spectrophotometer from KBr pellets. ^1H NMR spectra were registered on a Tesla BS-587A spectrometer (100 MHz), internal reference TMS, chloroform-d_1 as a solvent. Mass spectra were obtained on a Hewlett Packard 5890/5972 instrument in the electron impact ionization mode with ionizing electrons energy of 70 eV (capillary column HP-5MS, 30 m × 0.25 mm, stationary phase 5% PhMe Silicone, 0.25 μm, evaporator temperature 250°C).

2,2'-Arylmethylenebis(3-hydroxy-5,5-dimethylcyclohex-2-enones) (XVII–XXII, XXV–XXX, XXXII, XXXV, XXXVI). A mixture of 0.01 mol of aldehyde **XI**–**XVI**, **XXIII**, **XXIV** or 0.005 mol of dialdehyde **VI**–**IX**, **XXXI**, **XXXIII**–**XXXIV**, 0.02 mol of dimedone **X**, 0.1 g of triethylamine, and 50 mL of anhydrous methanol was refluxed for 1 h. Then the reaction mixture was cooled to 0–5°C. The desired products were filtered through a glass porous filter, washed with cold methanol, and dried in air for 6–8 h.

Compound XXV. IR spectrum, ν, cm^{-1}: 3131 ($CH_{isoxazole}$); 3061, 3043 (CH_{Ar}); 2959, 2931, 2888, 2872 (CH_{aliph}); 1594 (C=O); 1619, 1579, 1499 ($C{=}C_{Ar}$); 1450 ($C{=}N_{isoxazole}$); 1262, 1231, 1139, 1040, 1008 (C–O); 896, 870, 848, 810, 764, 740, 724 (CH_{Ar}). ^1H NMR spectrum, δ, ppm: 1.14 s (12H, 4Me), 2.38 s (8H, $4CH_2$), 5.41 s (1H, CH), 6.17 s (1H, $CH_{isoxazole}$), 7.40 m ($3H_{Ar}$), 7.70 d ($2H_{Ar}$, ^3J 8 Hz), 12.23 br.s (2H, OH). ^{13}C NMR spectrum, δ_C, ppm: 27.99 (Me), 46.59 (CH_2), 99.31 ($CH_{isoxazole}$); 125.83, 128.92, 130.07 (CH_{Ar}); 31.53, 114.12, 127.53, 163.07, 169.66 (C_{tert}); 189.91 (C=O).

Compound XXVI. IR spectrum, ν, cm^{-1}: 3134 ($CH_{isoxazole}$); 3087, 3058, 3034 (CH_{Ar}); 2959, 2929, 2888, 2871 (CH_{aliph}); 1592 (C=O); 1615, 1511, 1468 ($C{=}C_{Ar}$); 1451 ($C{=}N_{isoxazole}$); 1262, 1231, 1139, 1040, 1008 (C–O); 896, 870, 848, 810, 764, 740, 724 (CH_{Ar}). ^1H NMR spectrum, δ, ppm: 1.14 s (12H, Me), 2.34 s (3H, $\underline{Me}C_6H_4$), 2.37 s (8H, $4CH_2$), 5.39 s (1H, CH), 6.12 s (1H, $CH_{isoxazole}$), 7.19 d ($2H_{Ar}$, ^3J 8 Hz), 7.58 d ($2H_{Ar}$, ^3J 8 Hz), 12.24 br.s (2H, OH). ^{13}C NMR spectrum, δ_C, ppm: 21.49 ($\underline{Me}C_6H_4$), 27.94 (Me), 46.54 (CH_2), 98.67 ($CH_{isoxazole}$); 125.72, 129.55 (CH_{Ar}); 31.48, 114.10, 124.82, 140.23, 163.07, 169.66 (C_{tert}); 189.83 (C=O).

Xanthenes XXXVII, XXXVIII. A mixture of 0.01 mol of **XVIII** or **XXII**, 0.5 g of sulfocationite FIBAN K-1, and 75 mL of benzene was refluxed with a Dean–Stark trap for 16–18 h. Next, sulfocationite was separated, and the solvent was removed. The target compound was purified by column chromatography on Al_2O_3 (60–100 μm, neutral, II Brockmann activity) eluting with benzene.

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