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MICHAEL REACTION IN SYNTHESIS OF 6-AMINO-4-(4-BUTOXYPHENYL)-3,5-DICYANOPYRIDINE-2(1H)-THIONE

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The reaction of 4-butoxybenzalcyanoacetic ester with cyanothioacetamide yielded 6-amino-4-(4-butoxyphenyl)-3,5-dicyanopyridine-2(1H)-thione, also synthesized by recyclization of 2,6-diamino-4-(4-butoxyphenyl)-3,5-dicyano-4H-thiopyran and condensation of 4-butyoxybenzaldehyde with a two-fold excess of cyanothioacetamide. Substituted 2-alkylthiopyridines and thieno[2,3-b]pyridines were obtained with the indicated pyridinethione.

Arylmethylcyanoacetic esters react with cyanothioacetamide in the presence of tertiary amines like Michael addition with subsequent cyclization of the adducts formed into 4-aryl-6-hydroxy-3,5-dicyanopyridine-2(1H)-thiones [1-3]. When 2-thienylidenecyanoacetic ester is used, this reaction takes place as Thorpe dimerization [4] with subsequent heterocyclization *in situ* of the enaminonitrile formed into 4-amino-6-oxo-5-(2-thienylidene)-3-cyano-5,6-dihydropyridine-2(1H)-thione [3]. The use of cyanoselenoacetamide as the CH acid results in the formation of 4-aryl-6-oxo-3,5-dicyanopyridine-2(1H)-selenones [5], whose structure was established by XSA in [6].

In view of the ambiguity of the reactions of arylmethylenecyanoacetic esters with cyanothioacetamide and the broad synthetic and biological possibilities of the polyfunctionally substituted 3-cyanopyridine-2(1H)-chalcogenones formed [7], we investigated the reaction of 4-butoxybenzalcyanoacetic ester (I) with cyanothioacetamide (II) in the presence of a 1½-fold excess of N-methylmorpholine (C), which unexpectedly led to the formation of 6-amino-4-(4-butoxyphenyl)-3,5-dicyanopyridine-2(1H)-thione (III).

In the first stage, the reaction takes place as Michael addition [4] with the formation of adduct (IV), which decomposes into 4-butoxybenzalcyanothioacetamide (V) and cyanoacetic ester, i.e., in the given case, the Michael reaction follows the pattern of exchange with methylene components [8]. Acrylonitrile (V) formed *in situ* reacts with unreacted thioamide II, which results in adduct (VI). The latter is heterocyclized in the reaction conditions with elimination of hydrogen sulfide and hydrogen and is converted into 6-amino-4-(4-butoxyphenyl)-3,5-dicyanopyridine-2(1H)-thione III with a yield of 38% on conversion to ester I (method A). Incorporation of a two-fold excess of cyanothioacetamide in the reaction increased the yield of target product to 85%, which confirms the proposed mechanism of the reaction examined above. In addition, product III can be obtained by the reaction of substituted acrylonitrile V, obtained by Knoevenagel condensation of 4-butoxybenzaldehyde (VII) with cyanothioacetamide II in the presence of N-methylmorpholine (method B) or by condensation of aldehyde VII with a two-fold excess of cyanothioacetamide II (method C), which also confirms the pathway of formation of thione III proposed above. The structure of compound III was demonstrated by spectral studies (see Experimental section) and synthesis from thiopyran VIII (method D), obtained in turn by three independent methods; one feature was the occurrence of the reactions via the same intermediate adduct (IX):

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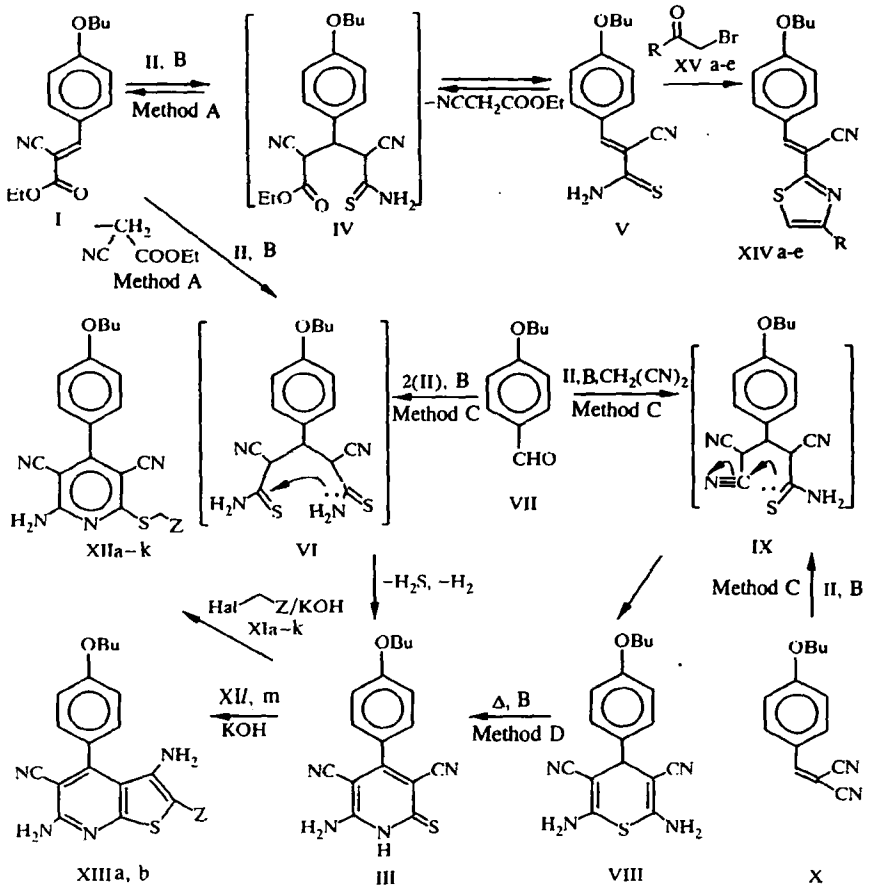

B = N-methylmorpholine

XI—XII a Hal = Br, Z = 4-ClC$_6$H$_4$; b Hal = Cl, Z = CH$_3$COO; c Hal = Br, Z = PhCO; d Hal = Br, Z = CH$_2$=CH; e Hal = Cl, Z = NH$_2$CO; f Hal = I, Z = H; g Hal = Br, Z = 4-BrC$_6$H$_4$CO; h Hal = Br, Z = 4-ClC$_6$H$_4$CO; i Hal = Cl, Z = EtCOO; j Hal = Cl, Z = PhCH$_2$COO; k Hal = Br, Z = 2-oxo-3-pyranylcarbonyl ; l Hal = Cl, Z = PhNHCO; m Hal = Cl, Z = CN; XIIIa Z = PhNHCO; b Z = CN; XIV, XV a R = 3,4-Cl$_2$C$_6$H$_3$; b R = 2-oxo-3-pyranyl ; c R = 4-BrC$_6$H$_4$; d R = 4-PhC$_6$H$_4$, e R = 4-ClC$_6$H$_4$

by the reaction of 4-butoxybenzalcyanothioacetamide V with malononitrile (method A), cyclocondensation of aldehyde VII with cyanothioacetamide II and malononitrile (method B), and the reaction of 4-butoxybenzalmalononitrile X with cyanothioacetamide II (method C).

Pyridinethione III is alkylated by halides (XIa-k) in DMF in the presence of an aqueous solution of KOH at the sulfur atom with formation of corresponding sulfides (XIIa-k). The use of a two-fold excess of KOH in alkylation of compound III results in the formation of substituted thieno[2,3-*b*]pyridines (XIIIa, b), which corresponds to the general characteristics of the chemistry of 3-cyanopyridine-2(1H)-thiones [7].

The structure of compound V was demonstrated by spectral methods (see Experimental section) and by obtaining thiazoles (XIVa-e) with the Hansch reaction [4]. The structure of compounds VIII, XIIa-k, XIIIa, b, and XIV a-e is in agreementwith the data from physicochemical and spectral methods of investigation (see Experimental section and Tables 1-4).

Convenient methods of synthesis of 6-amino-4-(4-butoxyphenyl)-3,5-dicyanopyridine-2(1H)-thione, used for preparation of substituted 2-alkylthiopyridines and thieno[2,3-*b*]pyridines, were thus developed based on the Michael reaction.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WP-100 SY (100 MHz) in solutions of DMSO-D_6 with TMS as internal standard. The IR spectra were made on an IKS-29 spectrophotometer in liquid petrolatum. The evolution of the reaction and purity of the compounds obtained were monitored by TLC on Silufol UV-254 plates in acetone–heptane system (3:5).

TABLE 1. Characteristics of 6-Amino-4-(4-butoxyphenyl)-3,5-dicyano-2-Z-methylthiopyridines XIIa-k

Compound	Found, %				Empirical formula	Calculated, %				mp, °C (solvent for crystallization)	Yield, %
	C	H	N	S		C	H	N	S		
XIIa	64,04	4,65	12,55	7,27	$C_{24}H_{21}ClN_4OS$	64,20	4,71	12,48	7,14	149...151 (AcOH)	83
XIIb	60,47	4,92	14,00	8,18	$C_{20}H_{20}N_4O_3S$	60,59	5,08	14,13	8,09	157...159 (methanol)	77
XIIc	68,02	4,88	12,05	7,38	$C_{25}H_{22}N_4O_2S$	67,85	5,01	12,66	7,25	159...161 (AcOH)	70
XIId	66,07	5,72	15,15	8,69	$C_{20}H_{20}N_4OS$	65,91	5,53	15,37	8,80	128...130 (1-butanol)	68
XIIe	60,02	4,89	18,19	8,36	$C_{19}H_{19}N_5O_2S$	59,83	5,02	18,36	8,41	178...180 (AcOH)	65
XIIf	64,00	5,51	16,42	9,33	$C_{18}H_{18}N_4OS$	63,88	5,36	16,56	9,47	176...178 (AcOH)	67
XIIg	57,37	3,92	10,61	6,24	$C_{25}H_{21}BrN_4O_2S$	57,59	4,06	10,74	6,15	184...186 (AcOH	80
XIIh	63,03	4,52	11,60	6,55	$C_{25}H_{21}ClN_4O_2S$	62,95	4,44	11,75	6,72	198...200 (ethanol)	83
XIIi	61,19	5,22	13,55	7,98	$C_{21}H_{22}N_4O_3S$	61,45	5,40	13,65	7,81	166...167 (ethanol)	78
XIIj	65,88	4,93	12,00	6,91	$C_{26}H_{24}N_4O_3S$	66,08	5,12	11,86	6,79	126...128 (methanol)	69
XIIk	65,65	4,19	11,04	6,36	$C_{28}H_{22}N_4O_4S$	65,87	4,34	10,97	6,28	237...239 (n-butanol – DMF (1 : 1))	85

TABLE 2. PMR and IR Spectral Data for Compounds XIIa-k

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm						
	NH_2	C ≡ N	δNH_2; C=O	NH_2 br.s	C_6H_4 d; d	SCH_2 s	OCH_2 t	$(CH_2)_2$ m	CH_3 t	Z
XIIa	3160, 3330, 3472	2208 sh	1620	8,09	7,10; 7,46*	4,47	4,03	1,30...1,80	0,92	7,46* (4H, d, C_6H_4)
XIIb	3222, 3345, 3450	2221 sh	1630, 1740	7,96	7,10; 7,49	4,21	4,07	1,30...1,84	0,95	3,70 (3H, s, CH_3)
XIIc	3220, 3333, 3410, 3450	2218, 2224	1653, 1710	8,06	7,09; 7,45	5,00	4,04	1,30...1,78	0,94	7,60 (5H, m, Ph)
XIId	3240, 3332, 3420	2225 sh	1630	8,01	7,10; 7,49	3,92 d	4,06	1,30...1,89	0,95	5,92 (1H, m, CH); 5,16 (1H, d, CH_2) and 5,41 (1H, d, CH_2)
XIIe	3195, 3330, 3433	2220	1630, 1680	8,00	7,09; 7,49	3,89	4,06	1,33...1,80	0,95	7,27 (2H, br. s, NH_2)
XIIf	3215, 3340, 3460	2220	1644	7,98	7,10; 7,49	2,58	4,06*[2]	1,28...1,82	0,95	(H)*[3]
XIIg	3200, 3334, 3430	2215 sh	1630, 1680	7,90	7,08; 7,48	4,95	4,04	1,34...1,90	0,93	8,00 (2H, d, Ar) and 7,77 (2H, d, Ar)
XIIh	3238, 3332, 3420	2222 sh	1644, 1700	7,87	7,10; 7,50	4,91	4,06	1,32...1,81	0,95	8,09 (2H, d, Ar) and 7,65 (2H, d, Ar)
XIIi	3226, 3320, 3405	2207 sh	1637, 1714	7,95	7,09; 7,48	4,18	4,08*	1,30...1,78	0,95	1,22 (3H, t, CH_3); 4,08 (2H, q, OCH_2)*
XIIj	3236, 3330, 3418	2208 sh	1640, 1725	7,93	7,10; 7,48	4,28	4,06	1,31...1,84	0,95	5,19 (2H, s, OCH_2); 7,35 (5H, m, Ph)
XIIk	3242, 3390, 3540	2220	1635, 1720	7,85	7,11; 7,50	4,80	4,06	1,33...1,78	0,96	8,77 (1H, s, 4-H); 7,70...8,01 (4H, m, H_{arom})

*The signals overlap.

*[2]Signal of the SCH_3 group.

*[3]See signal of SCH_3 group.

TABLE 3. Characteristics of Substituted Acrylonitriles XIVa-e

Compound	Found, %				Empirical formula	Calculated, %				mp, °C	Yield, %
	C	H	N	S		C	H	N	S		
XIVa	61,33	4,11	6,62	7,59	$C_{22}H_{15}Cl_2N_2OS$	61,54	4,23	6,52	7,47	128...130	88
XIVb	69,89	4,58	6,63	7,65	$C_{25}H_{20}N_2O_3S$	70,07	4,70	6,54	7,48	154...155	93
XIVc	59,95	4,14	6,45	7,51	$C_{22}H_{19}BrN_2OS$	60,14	4,36	6,38	7,30	109...111	75
XIVd	76,89	5,63	6,51	7,18	$C_{28}H_{24}N_2OS$	77,06	5,50	6,42	7,36	115...117	79
XIVe	67,10	4,99	6,98	8,00	$C_{22}H_{19}ClN_2OS$	66,91	4,85	7,09	8,12	85...86	80

TABLE 4. PMR Spectral Data for Compounds XIVa-e

Compound	CH= S	$H_{thiazolyl}$ s	C_6H_4 d; d	OCH_2 t	$(CH_2)_2$ m	CH_3 t	R
XIVa	8,31	8,16	7,96; 7,05	4,04	1,25...1,90	0,93	7,76 (1H, d); 7,80 (2H, m)
XIVb	8,44	8,22	8,02; 7,07	4,07	1,15...1,82	0,94	8,78 (1H, s); 7,30...7,89 (4H, m)
XIVc	8,27	8,21	7,95; 7,09	4,05	1,22...1,78	0,92	8,08 (2H, d); 7,64 (2H, d)
XIVd	8,26	8,10	8,00; 7,13	4,10	1,30...1,76	0,97	7,49...7,85 (9H, m)
XIVe	8,27	8,22	8,02;* 7,09	4,05	1,28...1,80	0,93	7,51 (2H, d); 8,02 (2H, d)*

*The signals overlap.

4-Butoxybenzalcyanothioacetamide (V). Here 2 g (20 mmole) of cyanothioacetamide II and 2 drops of N-methylmorpholine were added to a solution of 3.5 ml (20 mmole) of 4-butoxybenzaldehyde VII in 15 ml of ethanol at 20°C and stirred for 30 min. The sediment of product V formed was filtered off and washed with ethanol and hexane. Yield of 4.9 g (94%). Yellow crystals. Mp = 131-132°C (from ethanol). IR spectrum: 3300, 3390 (NH_2), 2220 (C≡N), 1648 cm^{-1} (NH_2). PMR spectrum: 9.98 (1H, br. s, NH_2) and 9.46 (1H, br. s, NH_2); 8.07 (1H, s, CH=); 7.97 d and 7.13 d (at 2H, C_6H_4); 4.09 (2H, t, OCH_2); 1.15-1.85 (4H, m, $2CH_2$); 0.94 ppm (3H, t, CH_3). Found, %: C 64.32; H 6.06; N 10.84; S 12.49. $C_{14}H_{16}N_2OS$. Calculated, %: C 64.59; H 6.19; N 10.76; S 12.32.

6-Amino-4-(4-butoxyphenyl)-3,5-dicyanopyridine-2(1H)-thione (III). A. Here 1.5 ml (15 mmole) of N-methylmorpholine was added to a suspension of 2.7 g (10 mmole) of ester I and 2 g (20 mmole) of cyanothioacetamide II in 20 ml of ethanol, stirred at 20°C for 3 h, and held at the same temperature for 24 h. Then a 10% aqueous solution of HCl was added to the reaction mixture to pH 5, it was filtered, and the filtrate was held for 24 h at 20°C. The sediment of product III formed was filtered off and washed with cold ethanol and hexane. Yield of 2.8 g (85%). Mp = 199-201°C (AcOH). IR spectrum: 3145, 3294, 3360 (NH_2), 2215 (C≡N), 1643 cm^{-1} (NH_2). PMR spectrum: 12.00 (1H, br. s, NH); 8.24 (2H, br. s, NH_2); 7.47 (2H, d, Ar) and 7.07 (2H, d, Ar); 4.05 (2H, t, OCH_2); 1.30-1.85 (4H, m, $2CH_2$); 0.95 ppm (3H, t, CH_3). Found, %: C 63.15; H 4.78; N 17.05; S 10.04. $C_{17}H_{16}N_4OS$. Calculated, %: C 62.94; H 4.97; N 17.27; S 9.88.

B. Here 1 g (10 mmole) of cyanothioacetamide II and 1.5 ml (15 mmole) of N-methylmorpholine were added to a suspension of 2.6 g (10 mmole) of compound V in 15 ml of ethanol at 20°C and stirred for 4 h, then held at room temperature for 24 h. Then a 10% aqueous solution of HCl was added to the reaction mixture to pH 5 and it was held for 24 h at 20°C. The sediment of product III was filtered off and washed with cold ethanol and hexane. Yield of 2.9 g (89%). The product obtained was identical to the sample synthesized with method A (mp, TLC).

C. Then 2 g (20 mmole) of cyanoacetamide II and 1.5 ml (15 mmole) of N-methylmorpholine were added to a solution of 1.7 ml (10 mmole) of 4-butoxybenzaldehyde VII in 15 ml of ethanol at 20°C, stirred for 4 h, and held at the same temperature for 24 h. The reaction mixture was treated as described in method B, and 2.4 g (73%) of thione III was obtained, identical to the samples synthesized by methods A and B (mp, TLC).

D. A suspension of 3.3 g (10 mmole) of thiopyran VIII in 15 ml of ethanol was boiled for 4 h in the presence of 1.5 ml (15 mmole) of N-methylmorpholine. The reaction method was treated according to method B, and 2.2 g (68%) of compound III, identical to the sample synthesized by method A (mp, IR spectrum), was obtained.

2,6-Diamino-4-(4-butoxyphenyl)-3,5-dicyano-4H-thiopyran (VIII). A. Here 0.66 g (10 mmole) of malononitrile and 1 drop of N-methylmorpholine were added to a suspension of 2.6 g (10 mmole) of 4-butoxybenzalcyanothioacetamide V in 15 ml of ethanol at 20°C and the reaction mixture was stirred for 4 h. The sediment of product VIII was filtered off and washed with ethanol and hexane. Yield of 2.9 g (89%). Mp = 156-158°C (ethanol). IR spectrum: 3192, 3308, 3414 (NH_2), 2185 sh (C≡N), 1635 cm^{-1} (NH_2). PMR spectrum: 7.14 (2H, d, Ar) and 6.90 (2H, d, Ar); 6.85 (4H, br. s, $2NH_2$); 4.19 (1H, s, 4-H); 3.95 (2H, t, OCH_2); 1.30-1.84 (4H, m, $2CH_2$); 0.93 ppm (3H, t, CH_3). Found, %: C 62.38; H 5.40; N 17.51; S 10.01. $C_{17}H_{18}N_4OS$. Calculated, %: C 62.55; H 5.56; N 17.16; S 9.82.

B. Then 1 drop of N-methylmorpholine was added to a suspension of 1.7 ml (10 mmole) of aldehyde VII, 1 g (10 mmole) of thioamide II, and 0.66 g (10 mmole) of malononitrile in 15 ml of ethanol at 20°C and stirred for 4 h. The sediment of product VIII was filtered off and treated according to method A. Yield of 2.5 g (78%). The product was identical to the sample obtained with method A (mp, TLC).

C. Here 1 g (10 mmole) of cyanothioacetamide and 1 drop of N-methylmorpholine were added to a solution of 2.3 g (10 mmole) of 4-butoxybenzalmalononitrile X in 15 ml of ethanol at 20°C and stirred for 4 h. Method A was then followed, producing 2.9 g (90%) of compound VIII, identical to the sample prepared with method A (mp, IR spectrum).

6-Amino-4-(4-butoxyphenyl)-2-Z-methylthio-3,5-dicyanopyridines (XIIa-k). Here 5.6 ml (10 mmole) of 10% aqueous solution of KOH was added to a solution of 3.24 g (10 mmole) of thione III in 8 ml of DMF while stirring and the reaction mixture was filtered through a paper filter into a beaker containing 10 mmole of the corresponding halide XI. The mass obtained was stirred for 3 h, then diluted with an equal volume of water, the sediment of product XII formed was filtered off and washed with water, ethanol, and hexane. The characteristics of synthesized compounds XIIIa-k are reported in Tables 1 and 2.

3,6-Diamino-4-(4-butoxyphenyl)-2-phenylcarbamoyl-5-cyanothieno[2,3-*b*]pyridine (XIIIa). In succession, 5.6 ml (10 mmole) of 10% aqueous solution of KOH and 1.7 g (10 mmole) of α-chloroacetanilide XI*l* were added to a solution of 3.24 g (10 mmole) of thione III in 10 ml of DMF while stirring, stirred for 1 h, then diluted with another 5.6 ml of KOH solution, and stirring was continued for 3 h. Then the reaction mixture was diluted with an equal volume of water, and the

sediment of product XIIIa was filtered off and washed with water, ethanol, and hexane. Yield of 3.2 g (71%). Mp = 118-120°C (AcOH). IR spectrum: 3210, 3305, 3480 (NH_2), 2220 (C≡N), 1658 cm^{-1} (CONH). PMR spectrum: 9.28 (1H, s, NH); 7.64 (2H, d, Ar) and 7.15 (2H, d, Ar); 7.25-7.50 (7H, m, Ph and $C_{(6)}-NH_2$); 5.88 (2H, br. s, $C_{(3)}-NH_2$); 4.06 (2H, t, OCH_2); 1.30-1.85 (4H, m, $2CH_2$); 0.96 ppm (3H, t, CH_3). Found, %: C 65.50; H 4.88; N 15.17; S 7.18. $C_{25}H_{23}N_5O_2S$. Calculated, %: C 65.63; H 5.07; N 15.31; S 7.01.

4-(4-Butoxyphenyl)-3,6-diamino-2,5-dicyanothieno[2,3-*b*]pyridine (XIIIb) was prepared from thione III and chloroacetonitrile XIm by the method described above for compound XIIIa. Yield of 2.9 g (81%). Mp = 238-240°C. IR spectrum: 3150, 3330, 3478 (NH_2), 2198, 2220 (C≡N), 1640 (NH_2). PMR spectrum: 7.96 (2H, br. s, $C_{(6)}-NH_2$); 7.48 (2H, d, Ar) and 7.18 (2H, d, Ar); 5.37 (2H, br. s, $C_{(3)}-NH_2$); 4.14 (2H, t, OCH_2); 2.52-2.92 (4H, m, $2CH_2$); 1.39 ppm (3H, t, CH_{23}). Found, %: C 62.82; H 4.90; N 19.09; S 8.71. $C_{19}H_{17}N_5OS$. Calculated, %: C 62.79; H 4.71; N 19.27; S 8.82.

3-(4-Butoxyphenyl)-2-(4-R-thiazol-2-yl)-acrylonitriles (XVa-e). Then 10 mmole of α-bromoketone XIV was added to a suspension of 2.6 g (10 mmole) of thioamide IV in 10 ml of DMF at 20°C and stirred for 1 h, then held for 24 h at the same temperature. The sediment of product XV formed was filtered off and washed with ethanol and hexane. The characteristics of compounds XVa-e are reported in Tables 3 and 4.

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