4-Substituted Aryl Bromides Coupling with 4-Methoxybenzene-1-thiol by Means of Copper Catalysts

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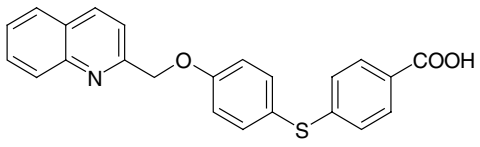
Received 3 February 2004

Synthesis of diaryl sulfides *via* nucleophilic coupling of the 4-substituted aryl bromides with 4-methoxybenzene-1-thiol is described. A radical-ionic mechanism of this coupling, carried out in the presence of heterogeneous copper catalysts, has been proposed. The reactivity of aryl bromides is correlated to the calculated values of electronic deficiency in position C-4 of the aromatic ring. The prepared compounds should be used as the leading building blocks of quinlukast higher homologues.

This is a follow-up paper to the previous article [1] where the inhibiting conditions of bis(4-methoxyphenyl)disulfide generation from 4-methoxybenzene-1-thiol by means of heterogeneous copper catalysts were discussed. This paper deals with the problem of the 4-substituted aryl bromides coupling with 4-methoxybenzene-1-thiol occurred during the preparation of higher homologues of quinlukast – VUFB 19363, which was patented for its multiple antileukotrienic activities [2]. Leukotrienes [3] are generated from arachidonic acid as a result of the 5-lipoxygenase action and play an important role in the inflammatory processes accompanying allergic diseases [4—8] of respiratory, gastrointestinal, and dermatological systems. Our work aimed at preparing the leading building blocks of quinlukast higher homologues.

Aryl thioethers could be synthesized from halides and inactivated halides by several methods: *i*) aromatic nucleophilic substitutions under vigorous heating in polar aprotic solvents at high temperatures [9—12]; *ii*) photoinitiation in polar aprotic solvents [13]; *iii*) catalysis by copper in polar and polar aprotic solvents [14—19], respectively; *iv*) reactions in mild conditions in the presence of $Pd(PPh_3)_4$ or palladium dibenzylideneacetone complex (Pd_2DBA_3) and bis(2-diphenylphosphinophenyl)ether (DPEphos) [20—27].



Heterogeneous copper catalysts were chosen for this coupling. Therefore, the radical-ionic mechanism has been proposed (Scheme 1). The reactions of 4-substituted aryl bromides with 4-methoxybenzene-1-thiol were performed under oxygen, nitrogen, or argon atmospheres in various solvents (EtOH, butan-2-one, hexan-2-one, DMF, xylene). Various types of heterogeneous copper catalysts (Cu(0), Cu(I), Cu(II)) of diverse electronic parameters (conductors, semiconductors, insulators) containing various types of anions (halides, oxides, sulfides, sulfate, carbonate, and phosphate) were used so far.

4-Methoxybenzene-1-thiol reactivity, especially its oxidation or dehydrogenation, on heterogeneous copper catalysts has been described [1]. We showed that Cu(0) and Cu(II) catalysts gave bis(4-methoxyphenyl)-disulfide in high yields. The use of Cu(I) catalysts, in particular sulfide, oxide, and iodide, in hexan-2-one and DMF provided good yields of products (Table 1). Similar types of nucleophilic substitution using cop-

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Table 1. Yields and Conditions of the Coupling and the Electronic Deficiency Calculated Values Charges in Position C-4 of the Aromatic Ring

Reactant	Product	Catalyst	Yield/%	Charges (0)[d]	Charges (+1)[e]
Ia	*Ib*	Cu_2O	96	−0.12	0.69
IIa	*IIb*	Cu_2O	91	−0.13	0.71
IIIa	*IIIb*	Cu_2O	91	−0.14	0.71
IVa	*IVb*	Cu_2O	0	−0.16	0.60
Va	*Vb*	Cu_2O	76	−0.16	0.67
VIa	*VIb*	Cu_2O	0[a]	−0.19	0.68
		Cu_2S	0		
		Cu_2I_2	0		
VIIa	*VIIb*	Cu_2O	73[b]	−0.15	0.71
		Cu_2S	69		
		Cu_2I_2	62		
VIIIa	*VIIIb*	Cu_2O	64	*f*	*f*
		Cu_2S	61		
		Cu_2I_2	55		
IXa	*IXb*	Cu_2O	0[c]	*f*	*f*
		Cu_2S	38		
		Cu_2I_2	32		

a) Methyl 2-(4-bromophenyl)acrylate was generated only (66 %), *b*) mixture of propionitrile (12 %) and acrylonitrile (61 %), *c*) *VIIIb* was generated only (23 %), *d*) atomic charges at a former position of the bromine in reactant, formal charge of a molecule 0, *e*) ibid., formal charge + 1, *f*) charges have not been calculated due to the size and flexibility of the system.

per(I) catalysts have been described in papers [16—19, 26]. More reactive iodo derivatives [16, 18, 19, 26] were not used in this study due to financial and stability concerns.

EXPERIMENTAL

All solvents used for the synthesis were of anal. grade. The solvents were dried and freshly distilled under argon atmosphere. Copper catalysts Cu_2O (powder, 97 % purity), Cu_2S (powder, 99 % purity), and Cu_2I_2 (powder, 99 % purity) were purchased from Sigma-Aldrich.

Compounds *Ia*—*Va* are commercially available (Fluka). Compounds *VIa* and *VIIa* were prepared by alkylation of *IVa* and *Va* with lithium diisopropylamide and CH_3I in THF under kinetic conditions [28, 29]. The reaction of the Wittig reagent [30] and aldehyde *Ia* provided ester *VIIIa*. The latter was then catalytically hydrogenated on 10 % $Pd/BaSO_4$ to give ester *IXa*. 4-Methoxyphenyl (4-bromophenyl)alkylthioimidates were formed in 3 % yield approximately, when nitriles *Va*, *VIIa* were submitted to the coupling, whereas compounds of the 4-methoxyphenyl {4-[(4-methoxyphenyl)sulfanyl]phenyl}alkylthioimidate type were not isolated.

Kieselgel 60, 0.040—0.063 mm (Merck, Germany) was used for flash chromatography. TLC was performed on Silufol UV 254 plates (Kavalier, Votice, Czech Republic). The plates were illuminated under UV (254 nm) and the spots then visualized using the solution of Bromthymol Blue in NaOH. Melting points were determined on a Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany). Elemental microanalyses were carried out on an automatic microanalyzer EA1110CE (CE Instruments, Milan, Italy). Infrared spectra were recorded with neat oils (for noncrystalline materials) and in KBr pellets (for crystalline materials) on an IR-spectrometer Nicolet Impact 400. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury-VX BB 300 (299.95 MHz for ^1H and 75.43 MHz for ^{13}C). Chemical shifts are given relative to internal $Si(CH_3)_4$.

Ab initio (DFT) calculations (geometry optimizations, charge calculations) were performed in Gaussian 98W [27] at the B3LYP/6-31+G(d) level [31]. Merz, Singh, and Kollman procedure [32, 33] was used for the calculation of the charges and polarizable conductor calculation (CPCM) solvation model [34], as implemented in Gaussian 98W, was used to simulate the DMF medium. The relative permittivity of 38.3 was used for DMF.

During geometry optimizations, a systematic mapping over all exocyclic torsions (3 orientations for each) was performed (a PM3 [35, 36] method for this was used in the case of compounds *IVa*—*VIIa*, followed by the full B3LYP reoptimization of the lowest-energy conformers). Atomic charges were calculated for the global minima found in this way.

General Procedure

4-Methoxybenzene-1-thiol (60.0 mmol) was added slowly to an ice-cool suspension of NaH (70.0 mmol, 60 % dispersion in mineral oil) in dry DMF (150 cm^3). The mixture was stirred for a few minutes until the

evolution of hydrogen gas stopped. Compounds *Ia*—*IXa* (40.0 mmol) and copper(I) catalyst (10.0 mmol) were then added, and the mixture was refluxed under argon for 3 h. The cooled mixture was poured onto ice and extracted with diethyl ether. The combined organic extracts were washed with aqueous ammonia (35 %) and water, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed at reduced pressure. Flash chromatography (F_C) on silica gel provided a pure product (Table 1).

4-[(4-Methoxyphenyl)sulfanyl]benzaldehyde (*Ib*)

F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 1 : 9$), gave a white crystalline compound. Yield 96 %, diethyl ether—petroleum ether ($\varphi_r = 1 : 3$), $R_f = 0.22$. M.p. = 46—46.5 °C. For $C_{14}H_{12}O_2S$ ($M_r = 244.31$) w_i(calc.): 68.83 % C, 4.95 % H, 13.12 % S; w_i(found): 68.91 % C, 4.99 % H, 13.09 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 2836, 1697 (CHO), 1591 (Ph), 1461 (OCH_3), and 1099 (S—Ph). ^{1}H NMR ($CDCl_3$), δ: 9.88 (s, 1H, CHO), 7.65—7.72 (m AA′BB′, 2H, H-2′, H-6′), 7.45—7.52 (m AA′BB′, 2H, H-2″, H-6″), 7.10—7.16 (m AA′BB′, 2H, H-3′, H-5′), 6.94—7.01 (m AA′BB′, 2H, H-3″, H-5″), and 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$), δ: 191.2, 160.8, 149.0, 137.0, 133.2, 130.0, 125.8, 120.7, 115.4, and 55.4.

1-{4-[(4-Methoxyphenyl)sulfanyl]phenyl}-ethanone (*IIb*)

F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 1 : 9$), gave a white crystalline compound. Yield 91 %, diethyl ether—petroleum ether ($\varphi_r = 1 : 3$), $R_f = 0.28$. M.p. = 37—37.5 °C. For $C_{15}H_{14}O_2S$ ($M_r = 258.33$) w_i(calc.): 69.74 % C, 5.46 % H, 12.41 % S; w_i(found): 69.84 % C, 5.44 % H, 12.11 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1679, 1356 (CO—CH_3), 1590 (Ph), 1461 (OCH_3), and 1100 (S—Ph). ^{1}H NMR ($CDCl_3$), δ: 7.74—7.84 (m AA′BB′, 2H, H-2′, H-6′), 7.44—7.52 (m AA′BB′, 2H, H-2″, H-6″), 7.06—7.14 (m AA′BB′, 2H, H-3′, H-5′), 6.92—7.02 (m AA′BB′, 2H, H-3″, H-5″), 3.85 (s, 3H, OCH_3), and 2.53 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 197.1, 160.6, 146.9, 136.8, 133.8, 128.8, 125.7, 121.3, 115.3, 55.4, and 26.4.

Methyl 4-[(4-Methoxyphenyl)sulfanyl]benzoate (*IIIb*)

F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 1 : 9$), gave a white crystalline compound. Yield 91 %, diethyl ether—petroleum ether ($\varphi_r = 1 : 4$), $R_f = 0.41$. M.p. = 76—77 °C. For $C_{15}H_{14}O_3S$ ($M_r = 274.50$) w_i(calc.): 65.67 % C, 5.14 % H, 11.69 % S; w_i(found): 65.77 % C, 5.10 % H, 11.70 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 1724 (ester), 1580 (Ph), 1462 (OCH_3), and 1110 (S—Ph). ^{1}H NMR ($CDCl_3$), δ: 7.80—7.90 (m AA′BB′, 2H, H-2′, H-6′), 7.43—7.52 (m AA′BB′, 2H, H-2″, H-6″), 7.04—7.12 (m AA′BB′, 2H, H-3′, H-5′), 6.91—7.00 (m AA′BB′, 2H, H-3″, H-5″), 3.87 (s, 3H, OCH_3), and 3.85 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 166.8, 160.6, 146.4, 136.7, 129.9, 126.6, 125.7, 121.5, 115.3, 55.4, and 52.0.

{4-[(4-Methoxyphenyl)sulfanyl]phenyl}-acetonitrile (*Vb*)

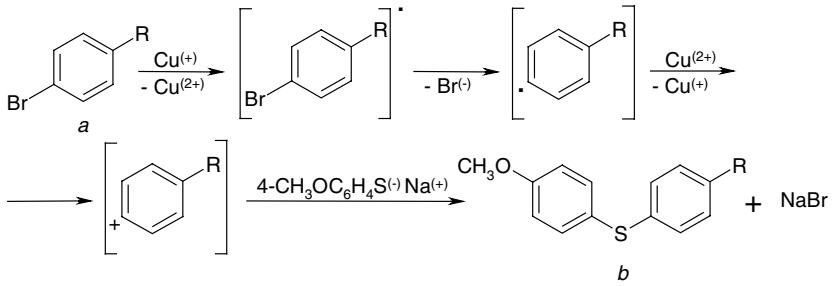
F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 3 : 7$), gave a light yellow crystalline compound. Yield 76 %, diethyl ether—petroleum ether ($\varphi_r = 1 : 2$), $R_f = 0.24$. M.p. = 38—38.5 °C. For $C_{15}H_{13}NOS$ ($M_r = 255.34$) w_i(calc.): 70.56 % C, 5.13 % H, 5.49 % N, 12.56 % S; w_i(found): 70.60 % C, 5.10 % H, 5.50 % N, 11.68 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 2250 (CN), 1591 (Ph), 1461 (OCH_3), and 1104 (S—Ph). ^{1}H NMR ($CDCl_3$), δ: 7.39—7.45 (m AA′BB′, 2H, H-2″, H-6″), 7.11—7.21 (m, 4H, H-2′, H-3′, H-5′, H-6′), 6.88—6.95 (m AA′BB′, 2H, H-3″, H-5″), 3.83 (s, 3H, OCH_3), and 3.68 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$), δ: 160.1, 139.3, 135.8, 128.4, 128.3, 127.0, 123.3, 117.7, 115.1, 55.4, and 23.1.

2-{4-[(4-Methoxyphenyl)sulfanyl]phenyl}-propionitrile (*VIIb*)

F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 3 : 7$), gave a light yellow crystalline compound. Yield 69 %, diethyl ether—petroleum ether ($\varphi_r = 2 : 3$), $R_f = 0.33$. M.p. = 34—35 °C. For $C_{16}H_{15}NOS$ ($M_r = 269.37$) w_i(calc.): 71.34 % C, 5.61 % H, 5.20 % N, 11.90 % S; w_i(found): 71.30 % C, 5.69 % H, 5.21 % N, 11.89 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 2973 (CH_3), 2254 (CN), 1591 (Ph), 1462 (OCH_3), and 1109 (S—Ph). ^{1}H NMR (DMSO), δ: 7.38—7.46 (m AA′BB′, 2H, H-2″, H-6″), 7.28—7.35 (m AA′BB′, 2H, H-3′, H-5′), 7.10—7.18 (m AA′BB′, 2H, H-2′, H-6′), 6.97—7.04 (m AA′BB′, 2H, H-3″, H-5″), 4.24 (q, 1H, $J = 7.14$ Hz, CH), 3.77 (s, 3H, OCH_3), and 1.48 (d, 3H, $J = 7.14$ Hz, CH_3). ^{13}C NMR (DMSO), δ: 160.0, 138.0, 135.7, 135.5, 128.3, 128.0, 122.8, 122.3, 115.6, 55.5, 29.5, and 20.7.

Ethyl (2*E*)-3-{4-[(4-Methoxyphenyl)sulfanyl]-phenyl}-2-methylacrylate (*VIIIb*)

F_C on silica gel, eluted with diethyl ether—petroleum ether ($\varphi_r = 1 : 9$), provided a white crystalline compound. Yield 64 %, diethyl ether—petroleum ether ($\varphi_r = 1 : 3$), $R_f = 0.47$. M.p. = 56.5—57.5 °C. For $C_{19}H_{20}O_3S$ ($M_r = 328.42$) w_i(calc.): 69.49 % C, 6.16 % H, 9.76 % S; w_i(found): 69.52 % C, 5.98 % H, 9.73 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 2971 (CH_3), 1734 (ester), 1639 (C═C), 1591 (Ph), 1462 (OCH_3), and 1110 (S—Ph). ^{1}H NMR ($CDCl_3$), δ: 7.60



R = *I*: -CHO
II: -COCH$_3$
III: -COOCH$_3$
IV: -CH$_2$COOCH$_3$
V: -CH$_2$CN
VI: -CH(CH$_3$)COOCH$_3$
VII: -CH(CH$_3$)CN
VIII: -CH=C(CH$_3$)COOC$_2$H$_5$
IX: -CH$_2$CH(CH$_3$)COOC$_2$H$_5$

Scheme 1. The general radical-ionic mechanism of nucleophilic coupling allowed through heterogeneous copper catalysts in polar or polar aprotic solvents, respectively. Aryl radical anions and changes in the oxidation numbers of copper catalyst are shown.

(bs, 1H, CH), 7.43—7.49 (m AA′BB′, 2H, Ar), 7.24—7.30 (m AA′BB′, 2H, Ar), 7.08—7.15 (m AA′BB′, 2H, Ar), 6.90—6.97 (m AA′BB′, 2H, Ar), 4.26 (q, 2H, J = 7.14 Hz, OCH$_2$), 3.84 (s, 3H, OCH$_3$), 2.09 (d, 3H, J = 1.37 Hz, CH$_3$), and 1.34 (t, 3H, J = 7.14 Hz, CH$_3$). ^{13}C NMR (CDCl$_3$), δ: 168.7, 160.2, 139.9, 138.0, 136.1, 133.0, 130.2, 128.1, 126.9, 122.9, 115.1, 60.9, 55.4, and 14.3.

Ethyl 3-{4-[(4-Methoxyphenyl)sulfanyl]-phenyl}-2-methylpropanoate (*IXb*)

F_C on silica gel, eluted with diethyl ether—petroleum ether (φ_r = 1 : 9), provided a colourless oil. Yield 38 %, diethyl ether—petroleum ether (φ_r = 1 : 3), R_f = 0.3. For $C_{19}H_{22}O_3S$ (M_r = 330.45) w_i(calc.): 69.06 % C, 6.71 % H, 9.70 % S; w_i(found): 69.05 % C, 6.76 % H, 9.71 % S. IR spectrum (neat), $\tilde{\nu}$/cm^{-1}: 2971 (CH$_3$), 2936 (CH$_2$), 1730 (ester), 1580 (Ph), 1462 (OCH$_3$), and 1110 (S—Ph). ^{1}H NMR (CDCl$_3$), δ: 7.43—7.49 (m AA′BB′, 2H, Ar), 7.24—7.30 (m AA′BB′, 2H, Ar), 7.07—7.15 (m AA′BB′, 2H, Ar), 6.90—6.96 (m AA′BB′, 2H, Ar), 4.25 (q, 2H, J = 7.14 Hz, OCH$_2$), 3.84 (s, 3H, OCH$_3$), 2.95—3.06 (m, 1H, CH), 2.53—2.76 (m, 2H, CH$_2$), 1.34 (t, 3H, J = 7.14 Hz, CH$_3$), and 1.13 (d, 3H, J = 6.87 Hz, CH$_3$). ^{13}C NMR (CDCl$_3$), δ: 176.0, 160.2, 138.0, 136.1, 134.9, 130.2, 128.6, 122.9, 115.1, 60.8, 55.4, 41.4, 39.1, 16.8, and 14.1.

RESULTS AND DISCUSSION

The 4-substituted aryl bromides *Ia*—*IXa* were used as the starting materials for coupling (Scheme 1).

Dry DMF was used as a solvent and powdered copper(I) oxide, copper(I) sulfide or copper(I) iodide were used as heterogeneous catalysts. Coupling of *IXa* with 4-methoxybenzene-1-thiol catalyzed by copper(I) oxide yielded *VIIIb* in 23 %. When *VIIa* was submitted to the coupling with 4-methoxybenzene-1-thiol on copper(I) oxide, the mixture of alkylated products was obtained in 73 % yield. The mixture could not be separated without the preparative HPLC. According to ^{1}H NMR the mixture contained 17 % of *VIIb* and 83 % of 2-{4-[(4-methoxyphenyl)sulfanyl]phenyl}acrylonitrile, ^{1}H NMR (CDCl$_3$), δ: 7.78 (d, 2H, J = 12.00 Hz, CH$_2$). Thus, copper(I) sulfide and copper(I) iodide, which do not possess dehydrogenation properties, were used for *VIIb* and *IXb* preparation. Coupling of *VIa* catalyzed by copper(I) oxide gave only methyl 2-(4-bromophenyl)acrylate in 66 % yield, ^{1}H NMR (CDCl$_3$), δ: 7.37 (d, 2H, J = 16.00 Hz, CH$_2$), but any coupling product (see Table 1). The coupling catalyzed by copper(I) sulfide or iodide has not yielded any product. Dehydrogenation properties of copper(I) oxide came into play in the course of the *VIa*, *VIIa*, *IXa* coupling reactions. Ester *IVa* has not yielded any coupling product, in spite of this fact, the coupling reaction was catalyzed by copper(I) oxide.

The reactivity of the aryl bromides *Ia*—*VIIa* was correlated to the calculated values of electronic deficiency in position C-4 of the aromatic ring (Table 1). Charges of compounds *VIIIa* and *IXa* have not been calculated due to the size and flexibility of the system. *Ab initio* point charges calculated by Gaussian 98W [33] and adjusted to electrostatic potential were used as a measure of electronic deficiency. A formal charge of 0 in Table 1 corresponds to a radical structure. Values for a nonradical intermediate are also included; in that case, the formal charge of a molecule must be + 1. The differences in the charges were smaller than we expected, nevertheless, it is evident that, with the exception of compounds *Va* and especially *IVa*, the yields of the substitution products correlate with the charges in position C-4. All charges correspond to a DMF solution. The presence of a solvent (DMF), however, had only a negligible effect on the calculated charge values, as proved by gas-phase calculations. The charges were also quite insensitive to geometries, as verified

with some other local minima structures. In spite of this fact, we can only speculate that some other factors came into play in the course of the *IVa* and *Va* coupling reactions.

Seven new sulfides were obtained by the reaction of 4-substituted aryl bromides with 4-methoxybenzene-1-thiol, as the leading building blocks of quinlukast higher homologues [37, 38]. Copper(I) oxide, copper(I) sulfide or copper(I) iodide were used as heterogeneous catalysts. Copper(I) sulfide and copper(I) iodide displayed lower catalytic activity in comparison with copper(I) oxide, but the latter dehydrogenated compounds in the position of carbon chain branching; it means, *VIIIb* was formed from *IXa*, methyl 2-(4-bromophenyl)acrylate from *VIa* and 2-{4-[(4-methoxyphenyl)sulfanyl]phenyl}acrylonitrile from *VIIa*. Products *b* could be converted one into another *via* various types of reactions; esters *IVb* and *VIb* failed to be prepared by this nucleophilic alkylation, but could be generated, *e.g.* with *Vb* and *VIIb* hydrolysis and following esterification. It was found that the substitution yields correlate to the charges at the reaction centre, the more positive values giving higher yields.

Acknowledgements. This study was supported by the Ministry of Education of the Czech Republic, Projects No. LN00B125, No. MSM 0021620822, and No. MSM 223300006.

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