SYNTHESIS OF FUNCTIONALIZED 4-ARYL-2,3 BIS (TRIFLUOROMETHANESULFONYLOXY) BENZOPHENONES, BASED ON SITE-SELECTIVE SUZUKI-MIYAURA CROSS-COUPLING REACTIONS OF 2,3,4-TRIS (TRIFLUOROMETHANESULFONYLOXY) BENZOPHENONE.

Nadi **E**leya
Department Of Chemistry, Collage Of Science, Zakho University,Kurdistan – region, Iraq.
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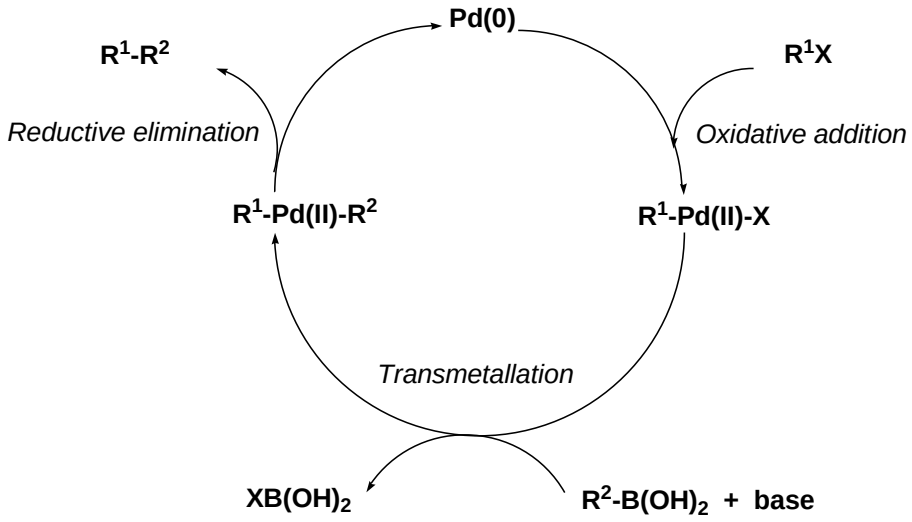
Abstract

Suzuki–Miyaura reactions of the tris(triflate) of 2,3,4-benzophenonewith one 1 equivalent of arylboronic acids afforded 4-aryal-2,3- bis(trifluoromethanesulfonyloxy)benzophenones with very good site selectivity favor of position C4 which is satirically less hindered than position C2.

Keywords: *benzophenones / Cross-coupling / Palladium / Regioselectivity.*

Introduction:

Suzuki–Miyaura coupling is widely used in organic synthesis to create carbon–carbon bonds.A general mechanism for the Suzuki-Miyaura cross coupling reaction of organic halides ortriflates with organoboron reagents usually involves three steps(Miyaura*et al*.1979). The first step is oxidative addition of organic halides or triflates to the Pd(0) complex to form anorganopalladium halide or triflates (R^1-Pd(II)-X). The second step istransmetallation with a boronic acid derivative to give a diorganopalladium complex (R^1-Pd-R^2). In the final step of the reaction, this complex undergoes a reductive elimination resulting in the formation of a carbon-carbon bond and regeneration of the catalyst(Geissler*et al*.1998)(Scheme 1).



Scheme 1. Catalytic cycle of the Suzuki reaction R^1, R^2 = alkyl, alkenyl, aryl, vinyl X= I, Br, Cl, OTf

Several catalysts are used for this reaction, e.g. Tetrakis (triphenylphosphine) palladium (0) $Pd(PPh_3)_4$and Tris (dibenzylideneacetone) dipalladium (0)Pd_2 $(dba)_3$ or Bis (triphenylphosphine) palladium(II) dichloride $Pd(PPh_3)_2$ Cl_2 or Palladium(II) acetate $Pd(OAc)_2$ together with phosphine ligands (such as triphenylphosphine (PPh_3), Tricyclohexylphosphine (PCy_3),2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (Suzuki *et al*.1998). A base such as carbonates, hydroxides, phosphates, or alkoxides are needed to accelerate the transmetallation step of the catalytic cycle (Suzuki*et al*.1998; Barder*et al*2005; Baxter*et al*.2005; Kingston*et al*. 2007). Brominated and iodinated aromatic compounds are favored over chlorinated counterparts due to lower reactivity of the C–Cl bond in the oxidative addition step(Miyaura*et al*1995; hassan*et al*.2002; Zhang*et al*.1998).A generally accepted reactivity order is I>OTf>Br>Cl(Nakano*et al*. 1997;Li*et al*. 2007).

In this project, my target was the synthesis of biarylbenzophenones derivatives based on siteselective using aryl triflates as electrophiles. These derivatives exhibit important pharmacological activities for example 4-arylbenzophenones exhibit interesting pharmacological properties, such as cytotoxic and antibacterial activity, and the inhibition of various enzymes(De Souza*et al*. 2001).unctionalizedbenzophenones are also widely used as photosensitizers and UV-filters (suncremes) (Cai *et al*. 2005).

Experimental Part:

General: Equipment, Chemicals and Work Technique:

NMR Spectroscopy

Bruker AC 250, Bruker ARX 300, Bruker ARX 500. For NMR characterization the one-dimensional ^{1}H NMR, proton-decoupled ^{13}C NMR, and DEPT 135 spectra were collected. If necessary, other techniques (NOESY, COSY, HSQC) were applied as well. All NMR spectra presented in this work were collected in $CDCl_3$ solution. All chemical shifts are given in ppm.

References (^{1}H NMR): TMS (δ = 0.00) or residual $CHCl_3$ (δ = 7.26) were taken as internal standard.

References (^{13}C NMR): TMS (δ = 0.0) or residual $CHCl_3$ (δ = 77.0) were taken as internal standard.

Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal.

Mass Spectrometry (MS)

AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV).

High Resolution Mass Spectrometry (HRMS)

Varian MAT 311, Intecta AMD 402.

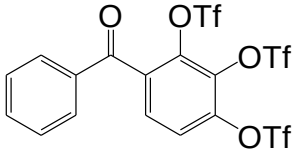
Melting Points

Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus), LeitzLabolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected.

Thin Layer Chromatography (TLC)

Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. **Column Chromatography**

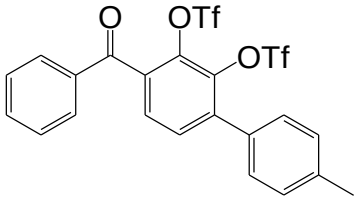
Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.200 mm, 70-230 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.



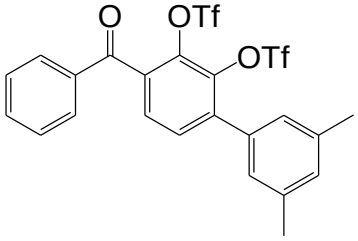
Synthesis of 2,3,4-Tris(trifluoromethanesulfonyloxy)-benzophenone (2):

To solution of2,3,4-trihydroxybenzophenone(**1**) (1.00 g, 4.34mmol) in CH_2Cl_2 (40 mL) was added pyridine (2.0 mL, 26.04mmol) and the solution was stirred at room temperature. To this solution was added Trifluoromethanesulfonic AnhydrideTf_2O (3.6 mL, 21.7mmol) and the solution was stirred at room temperature for 10 min. Subsequently, the solution was stirred at 40 °C for 1 hour. After cooling, the reaction mixture was concentrated in vacuo. Product **2** was isolated by rapid column chromatography (flash silica gel, heptane–EtOAc) as a white solid (2.1 g, 80%), mp 170–173 °C.[1] H NMR (300 MHz, $CDCl_3$): δ = 7.49-7.44 (t,J = 6.0 Hz 2H, ArH), 7.64-7.59 (m, 2H, ArH), 7.73-7.68 (m, 3H, ArH).^{13}C-NMR (69.4 MHz, $CDCl_3$): δ= 122.5, 128.9, 130.1, 130.8 (CH), 133.6, 134.3 (C), 134.5 (CH), 135.0, 140.2, 143.6 (C), 189.5 (CO). ^{19}FNMR (282 MHz, CDCl3): -72.42, -72.47, -72.71.GC-MS (EI, 70 eV): *m/z* (%) = 626 ([M]$^+$, 10), 296 (7), 105 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_8F_9$ $O_{10}S_3$ [M]$^+$: 626.91304, found 626.911395.

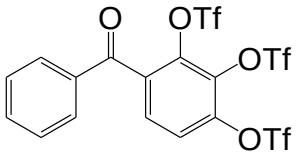
General Procedure for synthesis of 4a-e: A 1,4-dioxane solution (3 mL) of **2**, K_3PO_4 (1.5 eq.), [$Pd(PPh_3)_4$] (3 mol%), and arylboronic acid **3** (1.0 eq.) was stirred at 60 °C for 8 h. After cooling to 20 °C, distilled water was added, the organic and the aqueous layers were separated, and the latter was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.



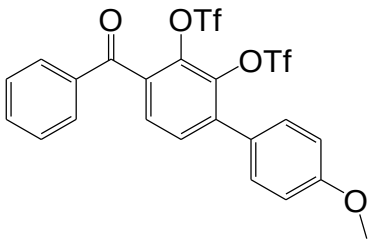
4-(*p*-tolyl)-2,3-bis(trifluorosulfonyloxy)-benzophenone(4a). Starting with **2**(100 mg, 0.159 mmol), *p*-tolylboronic acid**3a** (22 mg, 0.159 mmol), $Pd(PPh_3)_4$ (5.5 mg, 3 mol%, 0.006 mmol), K_3PO_4 (50 mg, 0.238 mmol), and 1,4-dioxane (3 mL),**4a** was isolated as a yellow oil (73 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 7.23 (d, J = 9.0 Hz 2H, ArH), 7,32 (d, J = 9.0 Hz 2H, ArH), 7.43 (t, J = 7.3 Hz 2H, ArH), 7.63-7.50 (m, 3H,ArH), 7.77-7.74 (m, 2H, ArH). ^{13}C-NMR (75.6 MHz, $CDCl_3$): δ= 21.3 (CH_3), 118.0 (q, J_{CF} = 319.0 Hz, CF_3), 118.3 (q, J_{CF} = 319.3 Hz, CF_3), 128.7, 129.1, 129.7, 130.8, 130.8, 131.1 (CH), 131.1, 133.1 (C), 134.0 (CH), 135.9, 138.8, 139.1, 139.9, 141.4 (C), 191.0 (CO).^{19}FNMR (282 MHz, CDCl3): -72.85, -73.65.GC-MS (EI, 70 eV): *m/z* (%) = 568 ([M]$^+$, 36), 435 (18), 302 (36), . HRMS (EI, 70 eV): calcd for $C_{22}H_{14}F_6O_7S_2$ [M]$^+$: 568.00796, found 568.008174.



4-(3´,5´-dimethylphenyl)-2,3-bis(trifluorosulfonyloxy)-benzophenone(4b): Starting with **2**(100 mg, 0.159 mmol), 3,5-dimethylphenylboronic acid**3b** (24 mg, 0.159 mmol), $Pd(PPh_3)_4$ (5.5 mg, 3 mol%, 0.006 mmol), K_3PO_4 (50 mg, 0.238 mmol), and 1,4-dioxane (3 mL),**4b** was isolated as a yellow oil (83 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 6H, $2CH_3$), 7.04 (br s, 3H, ArH), 7.43 (t, J = 7.4 Hz 2H, ArH), 7.62-7.50 (m, 3H, ArH), 7.77-7.75 (m, 2H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ= 21.0 ($2CH_3$), 118.0 (q, J_{CF} = 319 Hz, CF_3), 118.3 (q, J_{CF} = 319 Hz, CF_3), 127.0, 128.7, 130.1, 130.4, 130.8, 131.2 (CH), 133.2, 113.8 (C), 134.0 (CH), 135.9, 138.7, 138.8, 139.0, 141.5 (C), 191.0 (CO).^{19}FNMR (282 MHz, CDCl3): = -72.8, -73.8. GC-MS (EI, 70 eV): *m/z* (%) = 583 ([M+H]$^+$,11), 582 ([M]$^+$,45), 449 (31), 316 (33), 315 (21)301 (17). HRMS (ESI-TOF/MS): calcd for $C_{23}H_{17}F_6O_7S_2$ [M+H]$^+$: 583.03144, found 583.03161.

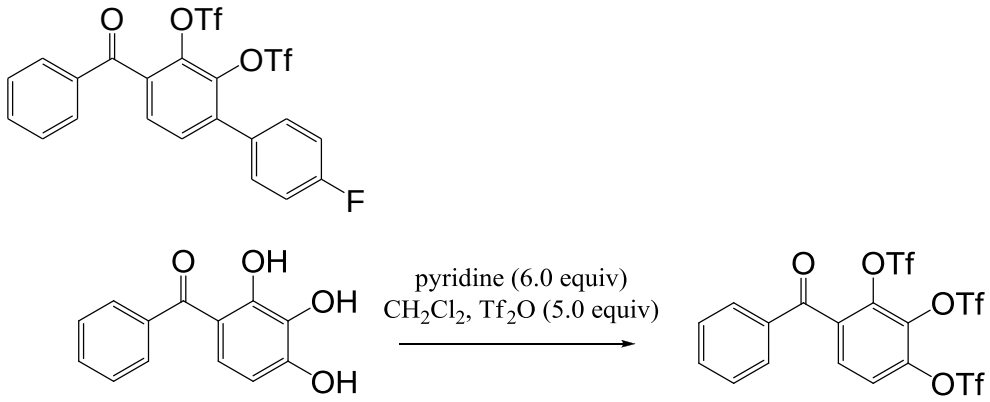


4-(4´-Ethylphenyl)-2,3-bis(trifluorosulfonyloxy)-benzophenone(4c): Starting with **2**(100 mg, 0.159 mmol), 4-ethylphenylboronic acid**3c** (24 mg, 0.159 mmol), $Pd(PPh_3)_4$ (5.5 mg, 3 mol%, 0.006 mmol), K_3PO_4 (50 mg, 0.238 mmol), and 1,4-dioxane (3 mL),**4c** was isolated as a yellow oil (74 mg, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.5 Hz, 3H, CH_3), 2.65 (q, J = 7.5 Hz, 2H, CH_2), 7.26 (d, J = 8.3 Hz, 2H, ArH), 7.34 (d, J = 8.3 Hz, 2H, ArH), 7.43 (t, J = 7.4 Hz 2H, ArH), 7.63-7.51 (m, 3H, ArH), 7.78-7.75 (m, 2H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ= 15.3 (CH_3), 28.6 (CH_2), 118.0 (q, J_{CF} = 321 Hz, CF_3), 118.3 (q, J_{CF} = 321.0 Hz, CF_3), 128.5, 128.6, 129.2, 130.1, 130.5, 130.8 (CH), 131.2, 133.1 (C), 134.0 (CH), 135.9, 138.8, 139.1, 141.4, 146.2 (C), 191.0 (CO).^{19}FNMR (282 MHz, CDCl3): = -72.8, -73.6. GC-MS (EI, 70 eV): *m/z* (%) = 583 ([M+H]$^+$,7), 582 ([M]$^+$,30), 449 (19), 316 (23), 315 (10), 288 (15), 187 (15). HRMS (EI, 70 eV): calcd for $C_{23}H_{16}F_6O_7S_2$ [M]$^+$: 582.02361, found 582.02232.



4-(4´-Methoxyphenyl)-2,3-bis(trifluorosulfonyloxy)-benzophenone(4d): Starting with **2**(100 mg, 0.159 mmol), 4-methoxyphenylboronic acid**3d** (24 mg, 0.159 mmol), $Pd(PPh_3)_4$ (5.5 mg, 3 mol%, 0.006 mmol), K_3PO_4 (50 mg, 0.238 mmol), and 1,4-dioxane (3 mL),**4d** was isolated as a yellow oil (71 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3H, OCH_3), 6.94 (d, J = 8.8 Hz, 2H, ArH), 7.43 (t, J = 7.4 Hz 2H, ArH), 7.60-7.47 (m, 3H, ArH), 7.77-7.75 (m, 2H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ= 55.3 (OCH_3), 114.5 (CH), 118.0 (q, J_{CF} = 321 Hz, CF_3), 118.3 (q, J_{CF} = 321.0 Hz, CF_3), 126.2 (C), 128.6, 130.1, 130.5, 130.6, 130.7 (CH), 132.8 (C), 134.0 (CH), 138.7, 139.1, 141.0, 160.7 (C), 191.0 (CO).GC-MS (EI, 70 eV): *m/z* (%) = 585 ($[M+H]^+$, 10), 584 ($[M]^+$,50), 452 (12), 451 (60), 318 (25). HRMS (EI, 70 eV): calcd for $C_{22}H_{14}F_6O_8S_2$ $[M]^+$: 584.00288, found 584.002987.

4-(4´-Fluorophenyl)-2,3-bis(trifluorosulfonyloxy)-benzophenone(4e): Starting with **2**(100 mg, 0.159 mmol), 4-fluorophenylboronic acid**3e** (22 mg, 0.159 mmol), $Pd(PPh_3)_4$ (5.5 mg, 3 mol%, 0.006 mmol), K_3PO_4 (50 mg, 0.238 mmol), and 1,4-dioxane (3 mL),**4e** was isolated as a yellow oil (68 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (t, J = 7.0 Hz 2H, ArH), 7.50-7.40 (m, 4H, ArH), 7.65-7.53 (m, 3H, ArH), 7.78-7.74 (m, 2H, ArH). ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ= 116.3 (d, J = 21.9 Hz) (CH), 118.0 (q, J_{CF} = 320.9 Hz, CF_3), 118.3 (q, J_{CF} = 321.7 Hz, CF_3), 128.7 (CH), 130.0 (d, J = 3.6 Hz) (C), 130.1, 130.6, 130.8, 131.3 (J = 8.5 Hz) (CH), 133.7 (C), 134.1 (CH), 135.7, 138.7, 139.1, 140.2 (C), 164.2 (d, $J_{F,C}$= 250.7 Hz) (CF), 190.8 (CO).GC-MS (EI, 70 eV): *m/z* (%) = 572 ($[M]^+$, 31), 306 (50), 305 (45). HRMS (EI, 70 eV): calcd for $C_{21}H_{11}F_7$ O_7S_2 $[M]^+$: 571.98289, found 571.982497.



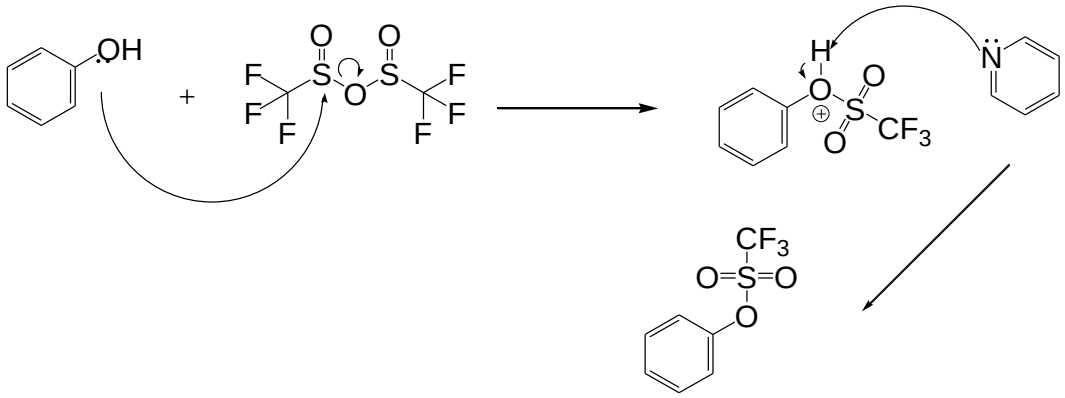
1 2

Scheme 2**.**Synthesis of 1,2,3-tris(trifluoromethanesulfonyloxy)-benzophenone (**2**).

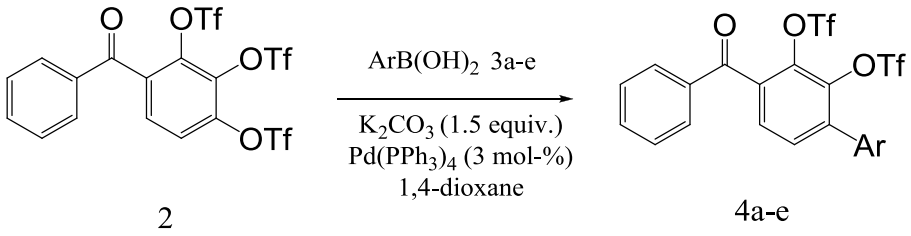
Results and discussions:

The reaction of commercially available 2,3,4-trihydroxybenzophenone (**1**) with Trifluoromethanesulfonic Anhydride Tf_2Oafforded 1,2,3-tris (trifluoromethanesulfonyloxy)-benzophenone (**2**) in 80% yield . The reaction was carried out at 40 °C for 1 hour (scheme 2).

The general mechanism for the reaction between the Phenol and Trifluoromethanesulfonic anhydride is explained below.



The Suzuki-Miyaura reaction of **2**with arylboronic acids **3** (1.0 equiv.) afforded the 4-aryl-2,3-bis(trifluorosulfonyloxy)-benzophenone**4**in 75-90% yield with very goodsite-selectivity (Scheme **3**). During the optimization, it proved to be importantto use exactly 1.0 equiv. of the arylboronic acid and to carry out the reaction at 60 °Cand to use 1,4-dioxane as a solvent for 8 h. Both electron-poor andelectron-rich arylboronic acids were successfully used.



Scheme 3. Synthesis of4-aryl-2,3-bis(trifluorosulfonyloxy)-benzophenone(**4a-e)**.
a= 4-MeC_6H_4, b= 3,5-MeC_6H_3, c= 4-(MeO)C_6H_4, d= 4-EtC_6H_4, e= 4-FC_6H_4.

The structure of product **2a**was elucidated by 2D NMR spectroscopy (NOESY, COSY,HSQC). As it's expected the first attack occurs at position number C4 which is sterically less hindered than position number C2 which is sterically more hindered. A NOESY correlation between hydrogen atoms H-5 with the*ortho*protons of the 4-methylphenyl group is diagnostic (Figure 1).

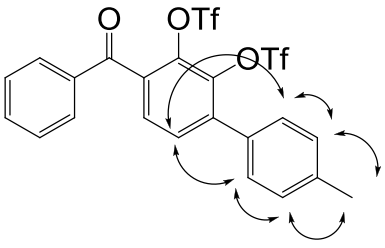
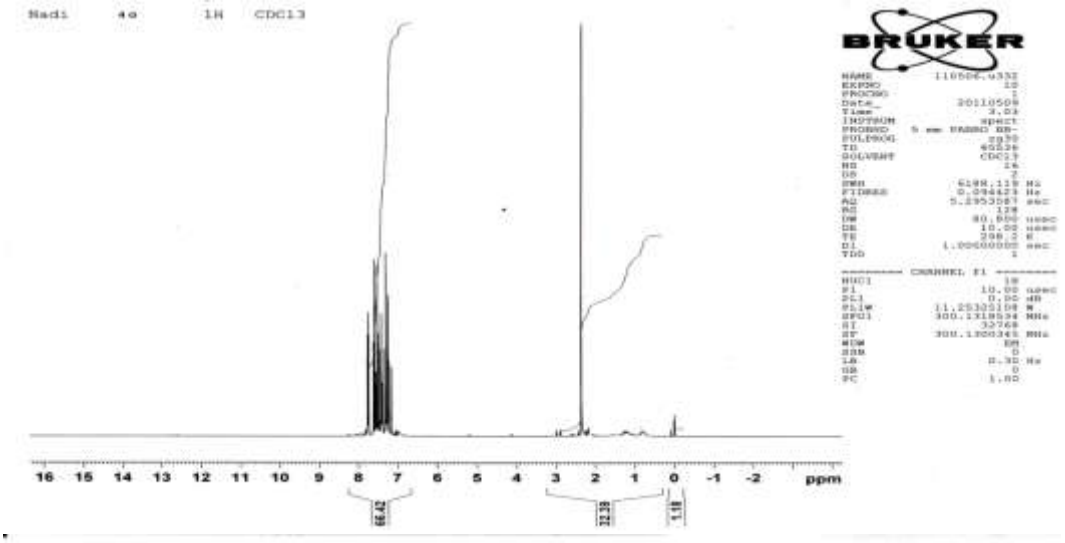
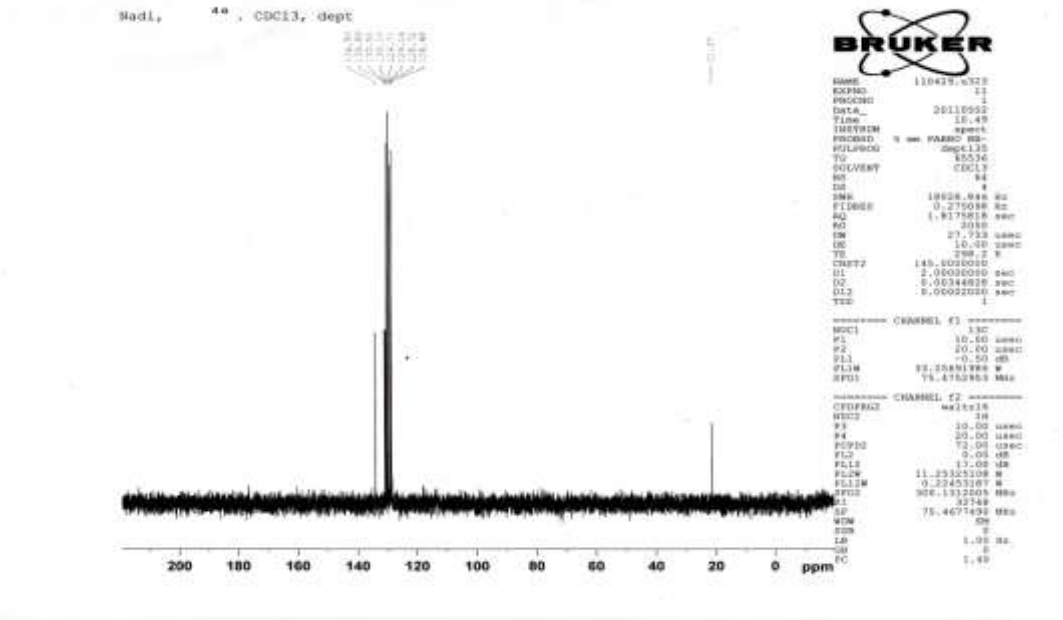
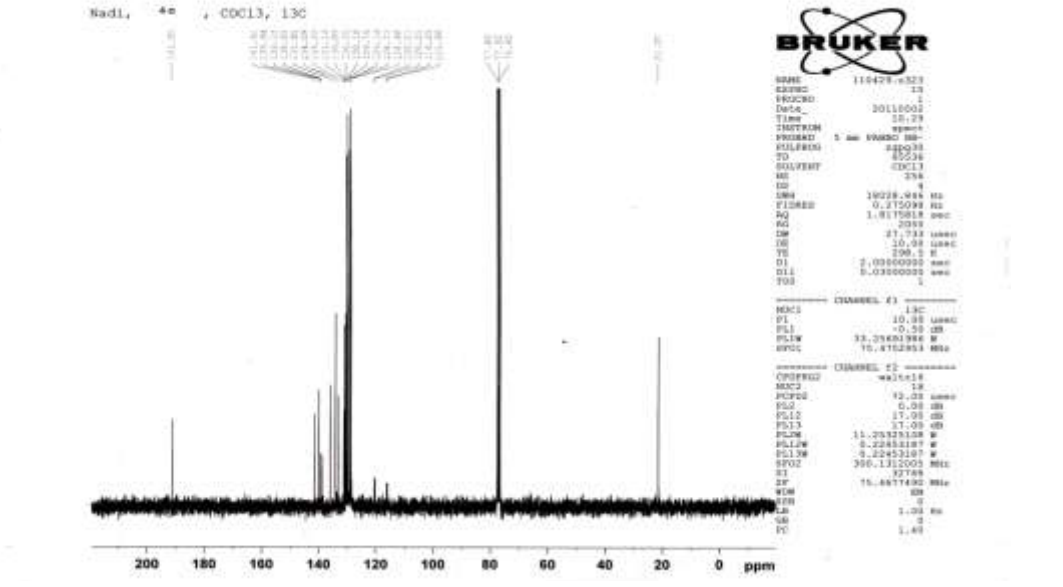
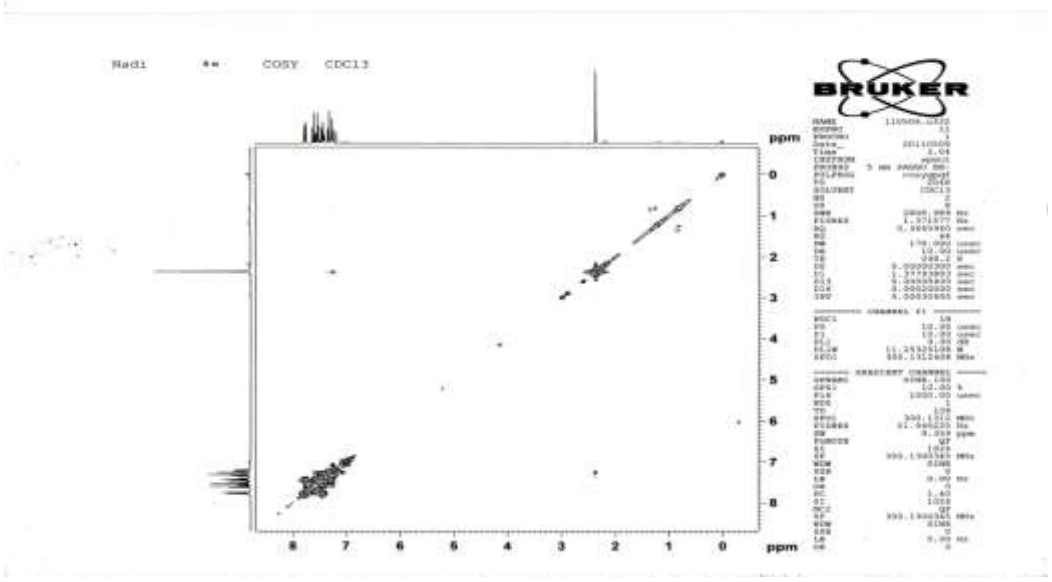


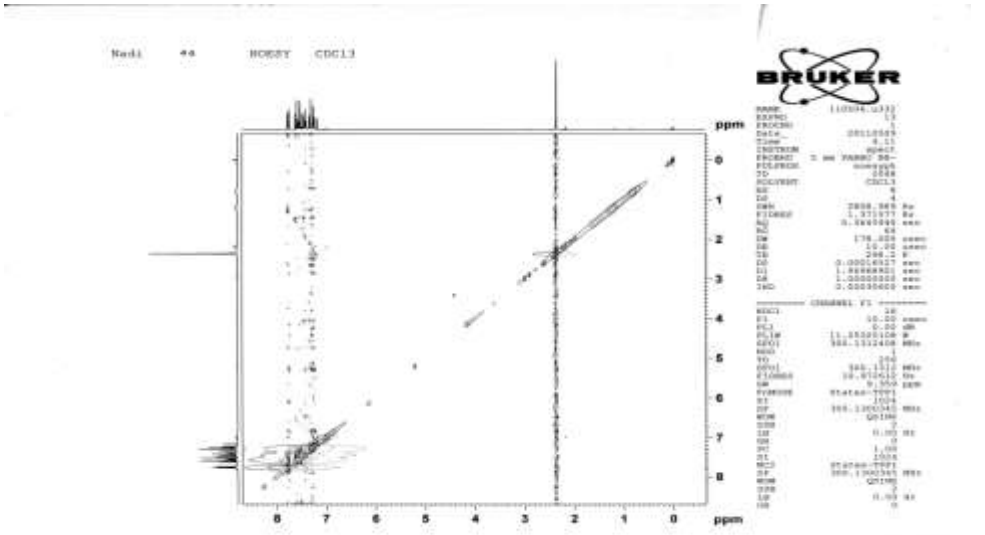
Figure1. Important NOESY correlations of **4a**
The spectra for compound **4a,** ^{1}HNMR, C^{13}, DEPT, COSY, NOSY, HSQC are arranged subsequently below.

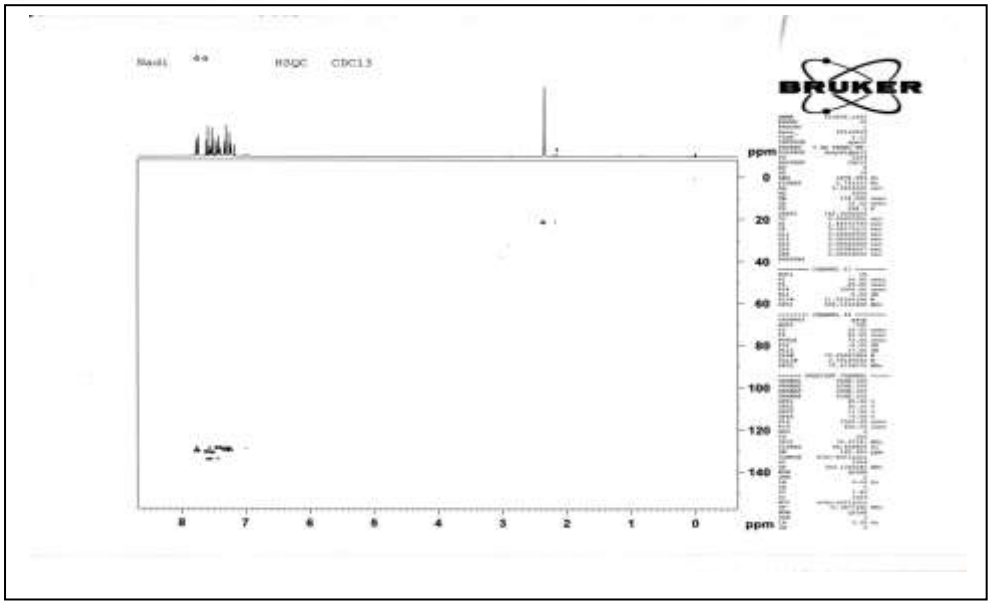

Nadi 4a 1H CDCl3
BRUKER
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
6.42
2.38
1.48


Nadi, 4a , CDCl3, dept
BRUKER
200 180 160 140 120 100 80 60 40 20 0 ppm


Nadi, 4a , CDCl3, 13C
BRUKER
200 180 160 140 120 100 80 60 40 20 0 ppm


Nadi 44 COSY CDCl3
BRUKER
ppm
8 7 6 5 4 3 2 1 0 ppm


Nadi 44 NOESY CDCl3
BRUKER
ppm
8 7 6 5 4 3 2 1 0 ppm


Nadi 44 HSQC CDCl3
BRUKER
ppm
0
20
40
60
80
100
120
140
8 7 6 5 4 3 2 1 0 ppm

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پێکهێنانا گهورینا 4-aryl-2,3-bis(trifluoromethanesulfonyloxy)benzophenones پشت بهستێ لسهر جهێ – باش هەلبژارتی دکەت، ئەوژی کالێکا (Suzuki-Miyura)یا خاچ – حەەابەەت یا (2,3,4- tris (trifluoromethanesulfonyloxy) benzophenone).

پوختە

کارێکا (Suzuki – Miyura) یا 2,3,4-tris(trifllate)-benzophenone دگەل ئێك هاوتا کێ شیا (aryl boronic acids) 4-aryl-2,3-bis(trifluoromethanesulfonyloxy)benzophenones.

گەلەك یا باشە دگەل جهەکێ گونجای لجهێ کاربونا ژمارە (4) ژبەرکو رێگرتنا دناڤ بوشایێ دا کێمترە ژجهێ کاربوونا ژمارە (2).

تحضير معوضات 4-اريل-3,2-داي (ثلاثي فلوروميثان سلفونيلوكسي) بنزو فينون بواسطه تفاعل اقتران سوزوكي-مايورا الانتقائي من مركب - ثلاثي الترفليت- بنزوفينون.

الخلاصة

تفاعل سوزوكي- مايورا لمركب4,3,2- ثلاثي الترفليت -بنزوفينون مع حامض الاريل بورنك يعطي مركبات 4-اريل-3,2-داي (ثلاثي فلوروميثان سلفونيلوكسي) بنزوفينون بتفاعل عالي الانتقائيه عند ذره الكاربون رقم 4 الاقل اعاقة فراغية.