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Full Paper

Efficient Asymmetric Synthesis of *S,S*-2-methylsulfanyl-2-methylsulfinyl-1-indanone

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Abstract: Diastereoselective synthesis of *SS*-2-methylsulfanyl-2-methylsulfinyl-1-indanol by reduction of SS-2-methylsulfanyl-2-methylsulfinyl-1-indanone optically enriched demonstrating to be highly efficiency using the sulfanyl group as asymmetric induction control agent during an addition reaction to carbonyl group.The 2-methylsulfinyl-1-indanone was obtained for the first time in one unique step without further oxidation steps. The synthesis of *SR*, *SS* of 2-methylsulphinyl-1-indanone optically enriched in good yield and good enantiomeric excess determined by nuclear magnetic resonance technique employing the Kagan reagent as chiral shift agent.

Keywords: asymmetric synthesis; indanone; indanol; phase-transfer catalysis

1. INTRODUCTION

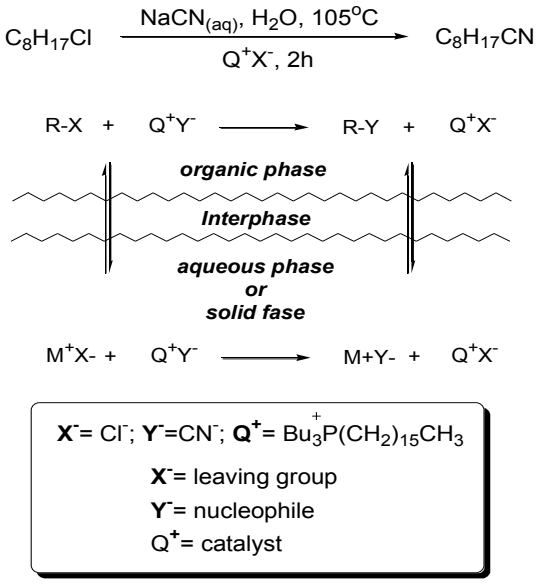
The term "phase-transfer catalysis" (PTC) was first used by Starks [1] in 1971 and can be defined as "a synthetic method that accelerates or causes reactions between substances that are placed in contact via one transfer agent or catalyst." [2] The transfer agent or catalyst is often an ammonium salt or quaternary phosphonium, usually called "quat" and symbolized by Q^+ (Q^+X^-). An example of such salts are tetrabutyl ammonium bromide $(C_4H_9)_4N^+Br^-$.

The first mechanistic proposal for the process of phase-transfer catalysis was formulated by Starks [1, 3] for a liquid-liquid system (LL-PTC) using a nucleophilic substitution reaction (Scheme 1).

This type of catalysis has wide range of applications, especially in nucleophilic substitution reactions and reactions involving deprotonation of weak organic acids [4].

It is estimated that, nowadays, the PTC is used in over 500 industrial processes, for example, in the production of pharmaceuticals, agrochemicals, polymers etc [5].

Other systems in addition to the (LL-PTC) [3] are used, such as solid-liquid (SL-PTC) [6] and gas-liquid (GL-PTC) [7] wherein the catalytic cycle occurs with the transfer between the two phases, analogous to that proposed for the liquid-liquid system.



Scheme 1. Mechanistic proposal for a nucleophilic substitution reaction via phase-transfer catalysis.

Among these types of catalysis is the asymmetric phase-transfer catalysis (APTC) which has used quaternary ammonium salts with defined

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stereogenic centers of asymmetric induction in organic compounds, for example, the salts (**1**) and (**2**) of alkaloids ephedra and (**3**) and (**4**) of the Cinchona [8] (Figure 1) have been used frequently and conducted at good results in terms of stereoselectivity, especially when the substituents in the quaternary nitrogen are bulky.

Although chiral ethers-crown are more resistant to decomposition and have been used successfully, for example, in asymmetric Michael addition reactions, their high cost makes impracticable their use in industrial scale [8].

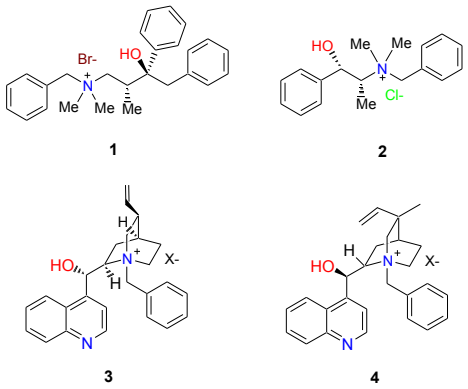
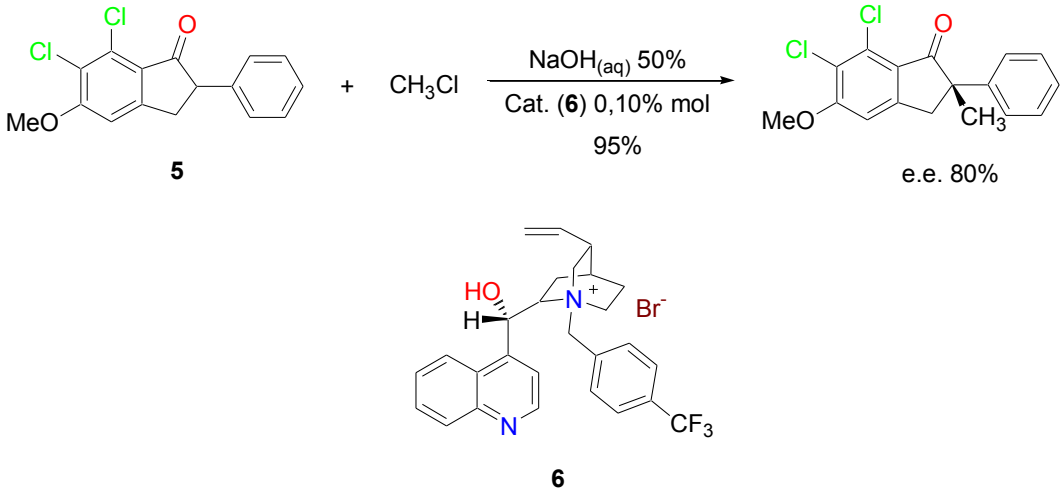


Figure 1. Salts derivated of the ephedra alcaloids: (**1**) and (**2**) and salts derivated of the cinchona (**3**) and (**4**).



Scheme 2. Methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone by asymmetric phase-transfer catalysis.

One of the best results in APTC reactions were obtained by Dolling [9] on the asymmetric methylation of 6,7-dichloro-5-methoxy- 2-phenyl-1-indanone (**5**) using as catalyst *N*-[(4-trifluoromethyl) benzyl] cinchoninium bromide (**6**) (Scheme 2).

The enantioselection mechanism proposed in this case is based on the formation of a chiral enolate of indanone (**5**) by the association of three points with the catalyst. In this mechanistic model, the formation of an intimate ionic-pair is guaranteed by a hydrogen bond between the hydroxyl group of the catalyst and the oxygen of the enolate by an interaction type π-π (aromatic ring of the enolate with the quinoline ring of the catalyst) and also other π-π interaction (benzyl ring of the catalyst with the phenyl group of the enolate) (Figure 2).

The association between the enolate and the catalyst must block one face of the enolate for the approximation of the electrophile, explaining the high values of enantiomeric excess. It is noteworthy that the mechanistic model proposed is supported by the stereochemistry of the obtained adducts.

The asymmetric phase-transfer catalysis proved to be a versatile method for inducing asymmetry in organic compounds; the literature contains several examples of the use of APTC in organic synthesis as sowed in the Table 1.

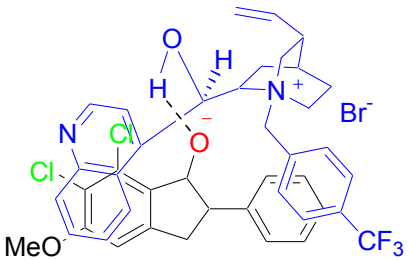
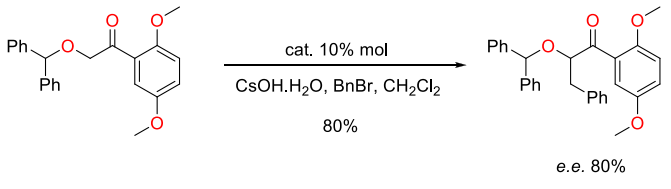
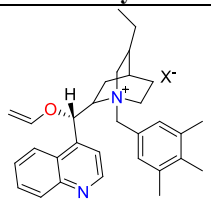
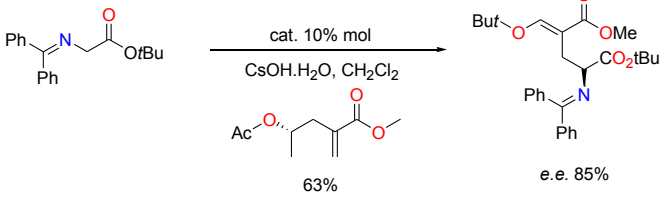
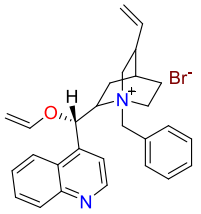
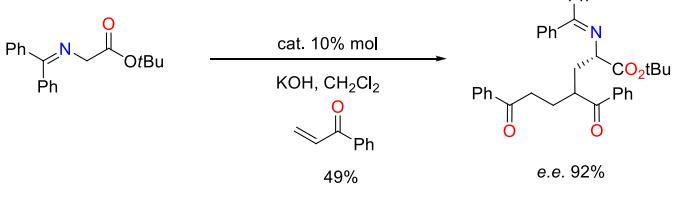
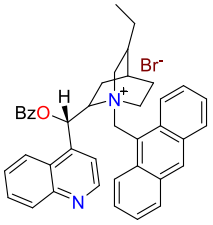
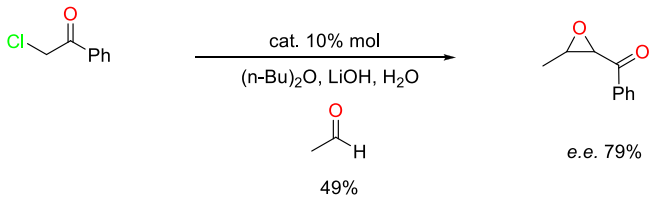
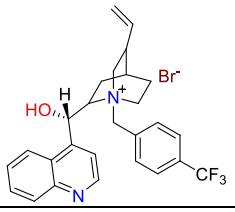


Figure 2. Methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone by asymmetric phase-transfer catalysis.

Among the synthetic reactions using APTC, the sulfanylation of β-sulfoxides have shown to be important because the obtained sulfoxides can be used

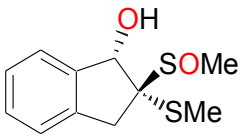
as chiral auxiliary in asymmetric synthesis [14, 15] and may be efficient as stereoselective inductors in reduction reactions, Diels-Alder reactions and the formation of C-C reactions [16-20]

Table 1. Some example of reactions catalyzed by APTC.

Reaction	Catalyst	Ref.
		[10]
		[11]
		[12]
		[13]

The efficiency of asymmetric induction is directly related to steric and electronic factors [17-20] between the groups attached in the sulfur atom. Thus, new methods for obtaining optically active sulfoxides are required for the synthesis of enantiomerically enriched compounds.

The α-hydroxy aldehydes and ketones proved to be very important precursors for the synthesis of biologically active compounds such as pheromones, ionophores and carbohydrates [21-23]. In this paper we present a synthetic study of *S,S*-2-methylsulfinyl-2- methylthio-1-indanol (**7**) enantiomerically enriched (Figure 3).



(**7**)

Figure 3. Structure of *S,*S-2-methylsulfinyl-2-methylthio-1-indanol.

2. MATERIAL AND METHODS

2.1. Materials

All reagents were purchased from Sigma-Aldrich and used without further purifications. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Inova 300 spectrometer (10% in $CDCl_3$ solutions) operating at 299.956 MHz and 75.418 MHz, respectively. Data processing was carried out on a Solaris workstation.

^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and coupling constants (*J*) are reported in Hz. The following abbreviations were used: s, d, q and m, for singlet, doublet, quartet and multiplet, respectively.

Thin layer chromatography was performed on glass-backed silica plates and visualized in UV-detection. The GC analysis were carried on Varian GC 431, equipped with CP 8944 column associated with Varian MS, model 210, using He as carrier gas.

The diastereomeric excess was obtained by

using of Kagan reagent.

2.2. Synthetic Procedures

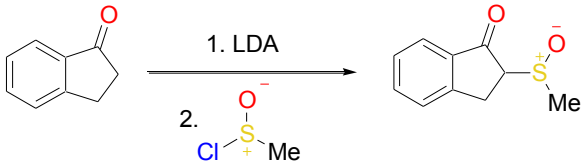
2.2.1 (±)-2-methylsulfinyl-1-indanone (**8**): A mixture of *n*-butyllithium (5 mL, 10.0 mmol), THF (60 mL) and lithium diisopropylamide (LDA) (1.0 g, 10.0 mmol) were stirred at 200 rpm for 5 min, after this time the reaction mixture was cooled until -78 ºC and added 1-indanone (1.32 g, 10.0 mmol) and stirred for 15 min, then, methanesulfinyl chloride (0.98 g, 10.0 mmol) was added. The mixture was stirred at 200 rpm for 2 hours and after this time, a saturated solution of sodium chloride (60 mL) was added and stirred at 200 rpm for 2 min. All of procedure occurred at room temperature. The organic phase was extracted with CH_2Cl_2 (3X 60 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The concentrate was purified by flash chromatography (silica, hexane/ether, 1:1, respectively) [24].

2.2.2 (±)-2-methylsulfanyl-2-methylsulfinyl-1-indanone (9): A mixture of (±)-2-Methylsulfinyl-1-indanone (0.19 g, 1.0 mmol), $CH_3SSO_2CH_3$ (0.126 g, 1.0 mmol), solid K_2CO_3 (0.27 g, 2,0 mmol), a solution of CH_2Cl_2/C_6H_6 1:1 (10 mL) and benzyltriethylamonium chloride (TEBAC) (0.022 g, 0.1 mmol) or *N*-benzylquininium chloride (QUIBEC) (0.090 g, 0.2 mmol) was stirred for 3 hours at room temperature. The reaction mixture was filtered concentrated under reduced pressure. The concentrate was purified by flash chromatography (silica, hexane/ether, 1:1, respectively) [25].

2.2.3 *S*,*S*-2-methylsulfanyl-2-methylsulfinyl-1-indanol (7): A mixture of methanol (15 mL), a solution of $NaBH_4$ (0.076 g, 2.0 mmol) in 3 mL of methanol and a diastereomeric mixture 17:1 of (±)-2-methylsulfanyl-2-methylsulfinyl-1-indanone (**9**) (0.242 g, 1.0 mmol) was stirred at 200 rpm during 1 hour at -78 ºC. After this time, was added a saturated solution of ammonium chloride (10 mL). The organic phase was extracted with CH_2Cl_2 (3 X 60 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The concentrate was purified by lixiviation using acetone [26].

3. RESULTS AND DISCUSSION

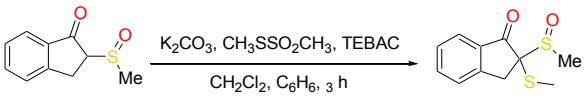
The keto sufoxide (**8**) was obtained adapting a synthetic method used for (±)-2-methylsulfinyl-1-tetralone [27] (Scheme 3).



Scheme 3. Synthesis of the keto sulfoxide (**8**).

The enolate from 1-indanone (generated in homogeneous phase, using LDA as the base) reacted with the methylsulfinyl chloride to form the keto sulfoxide in one step [28]. Is noteworthy that this is the first time that this reaction without the oxidation step [29] is reported in the literature. This method avoided the formation of disulfanilated product in the first step and conducted to the product (**8**) in 65% yield and 59% of diastereomeric excess, calculated from the integration of the ^{1}H-NMR signals corresponding to methylsulfinyl group in 2.88 and 2.59 ppm.

Initially, the sulfanylation reaction of the sulfinylated derivative (**8**) was tested in APTC conditions using TEBAC as catalyst, K_2CO_3 as base, *S*-methylmethanethiolsulfonate as the sulfanylating agent and a CH_2Cl_2/C_6H_6 1:1 as solvent (Scheme 4) [29]. The sulfanylation of racemic mixture of 2-methylsulfinyl-1-indanone in these conditions was monitored by TLC and after 3 hours the reaction finished.



Scheme 4. Sulfanylation reaction of 2-methylsulfinyl-1-indanone (**8**).

After purification, the 2-methylsulfanyl-2-methylsulfinyl-1-indanone was obtained in 84% yield and 73% of diastereomeric excess. The majority diastereoisomer was isolated by TLC in 55 % yield. The ^{1}H-NMR spectra for the majority diastereoisomer showed 2 siglets in 2.82 and 2.34 ppm that corresponds to methylsulfinyl and methylsulfanyl groups respectively [30]. The X-ray to the same compound obtained under scalemic form demonstrated to be the *CS*, *SS* diastereoisomer (Figure 4).

Aiming to improve the yield of the reaction we tested the same APTC conditions replacing TEBAC by QUIBEC as catalyst. In this case, the obtained yield was 93% and 73% of diastereomeric excess. It is noteworthy that the majority diastereoisomer formed was the same in the case of the reaction catalyzed by TEBAC.

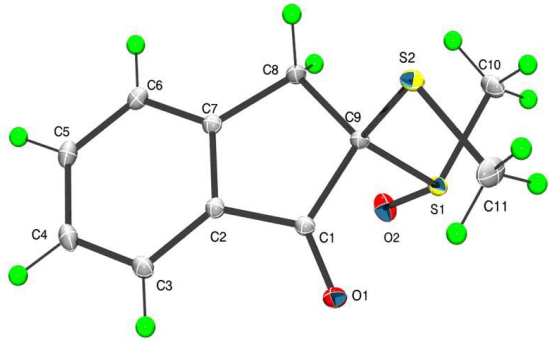
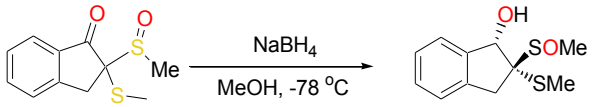


Figure 4. X-ray projection of (CS, SS) component of the pair of the 2-methylsulfanyl-2-methylsulfinyl-1-indanone racemic compound.

For comparison with homogeneous conditions, we establish the sulfanylation reaction of (**8**) using LiOH as base, CH_2Cl_2 as solvent and *S*-methylmethanethiolsulfonate as the sulfanylating agent. In this case, the reaction occurred faster than the first condition, and it was finished in 1 hour. The yields obtained were 93% and 90% diastereomeric excess.

The reduction of *S,S*-2-methylsulfanyl-2-methylsulfinyl-1-indanone (diastereoisomer mixture 10:0.8) using $NaBH_4$ was performed in metanol as solvent, isolating a unique diastereoisomer (**10**) in 70% yield and 90% of diastereomeric excess (Scheme 5).



(**9**) (**7**)

Scheme 5. Reduction reaction of (±)-2-methylsulfanyl-2-methylsulfinyl-1-indanone (**9**).

The hydrogen bonded to C-1 was observed in the ^{1}H-NMR spectra, in the form of doublet at 5.58 ppm (*J*=12 Hz).

4. CONCLUSION

In this paper we demonstrated the asymmetric synthesis *SR* or *SS* of 2-methylsulfanyl-2-methylsulfinyl -1-indanone (**9**) optically enriched in good yield, but in excellent diastereomeric excess determined by nuclear magnetic resonance technique employing the Kagan reagent as chiral shift reagent.

Therefore, we showed the diastereoselective synthesis of *S,S*-2-methylsulfanyl-2-methylsulfinyl-1-indanol (**7**) by reduction reaction using 2-methylsulfanyl-2-methylsulfinyl-1-indanone (**9**) optically enriched demonstrating the high efficiency of the sulfoxide group on the control of asymmetric induction in the carbonyl addition reaction.

5. ACKNOWLEDGMENTS

The authors thank to the Fundação de Apoio ao Desenvolvimento de Ensino, Ciência e Tecnologia do Estado do Mato Grosso do Sul (Fundect), to the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for the financial support and fellowships offered for this research.

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[24] *SS*-2-methylsulfinyl-1-indanone (**8a**): [α] 25D -73 (c = 1, CH_2Cl_2), m.p. 137-138 ºC, ^{1}H NMR (200 MHz, CDCl 3) (ppm): 2.88 (s, 3H, CH_3), 3.49 (dd, 1H, J=18, J=7.8), 3.79 (dd, 1H, J=18, J=3.0), 3.86 (dd, 1H, J=7.8, J=3.0), 7.43(dt, 1H, Ar, J=7.3), 7.56 (dd, 1H, Ar, J=7.3), 7.67 (dt, 1H, Ar, J=7.3 and 1.2), 7.78 (dd, 1H, Ar, J= 7.3) TOF MS ES$^+$ M/z calc.: 195.05, found: 195.03. *SR*-2-methylsulfinyl-1-indanone (**8b**): [α]25D +57 (c = 1, CH_2Cl_2) m.p. 136-138 ºC, ^{1}H NMR (200 MHz, $CDCl_3$) 2.88 (s, 3H, CH_3), 3.49 (dd, 1H, J=18, J=7.8), 3.79 (dd, 1H, J=18, J=3.0), 3.86 (dd, 1H, J=7.8, J=3.0), 7.43(dt, 1H, Ar, J=7.3), 7.56 (dd, 1H, Ar, J=7.3), 7.67 (dt, 1H, Ar, J=7.3 e 1.2), 7.78 (bd, 1H, Ar, J= 7.3), TOF MS ES$^+$ M/z calc.: 195.05, found: 195.03.

[25] *CS*,*SS*-2-methylsulfanyl-2-methylsulfinyl-1-indanone (**9a**): colorless solid, m.p. 96-98 °C, [α]25D + 78 (c = 1, CH_2Cl_2), ^{1}H NMR (200 MHz, $CDCl_3$) (ppm): 2.34 (3H, s), 2.82 (3H, s), 3.02 (1H, d, J = 18 Hz), 4.11 (1H, d, J = 18 Hz), 7.39 (dt, 1H, Ar, J=7.6), 7.49 (dd, 1H, Ar, J= 7.6), 7.64 (dt, 1H, Ar, J= 7.6), 7.80 (dd, 1H, Ar, J=7.6) ^{13}C NMR (ppm): 12.1, 32.1, 33.8, 70.0, 125.0, 126.3, 128.2, 134.2, 135.6, 150.4, 196.1. TOF MS ES$^+$ M/z calc.: 241, 03 found: 241,0385. *CR*,*SR*-2-methylsulfanyl-2-metilsulfinyl-1-indanone (**9b**); colorless solid, [α]25D -86 (c = 1, CH_2Cl_2), m.p. 95- 98 °C, ^{1}H NMR (200 MHz, $CDCl_3$) (ppm): 2.34 (3H, s), 2.82 (3H, s), 3.02 (1H, d, J = 18 Hz), 4.11 (1H, d, J = 18 Hz), 7.39 (dt, 1H, Ar, J=7.6), 7.64 (dt, 1H, Ar, J=7.6), 7.80 (dd, 1H, Ar, J=7.6)) ^{13}C NMR (ppm): 12.1, 32.1, 33.8, 70.0, 125.0, 126.3, 128.2, 134.2, 135.6, 150.4, 196.1. TOF MS ES+ M/z calc.: 241, 03 found: 241,03.

[26] *Ss*-2-methylsulfanyl-2-metilsulfinyl-1-indanol: colorless liquid, [α]25D + 7 (c = 1, D_2O) ^{1}H NMR (200 MHz, $CDCl_3$) (ppm): 2.74 (3H, s), 2.21 (3H, s), 5.59 (1H, s), 5.87 (1H, wide singlet, change with D_2O), 2.85 (1H, d , J = 14 Hz), 3.07 (1H, d, J = 14 Hz), 7.17-7.41 (4H, m, Ar). ^{13}C NMR (50 MHz, D_2O) (ppm): 13.01, 34.08, 33.77, 76.42, 78.18, 124.37, 124.54, 127.83, 128.76, 136.62, 141.80. E. A. calc.: C = 54.51 % H= 5.82%, found: C = 54.59 % H= 6.21%.

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