Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4849–4853

A short synthesis of highly substituted furans from alkenyl aryl ketones with dichloromethyl phenyl sulfoxide

Toshifumi Miyagawa and Tsuyoshi Satoh*

Department of Chemistry, Faculty of Science, Tokyo University of Science, Ichigaya-funagawara-machi 12, Shinjuku-ku, Tokyo 162-0826, Japan

Received 23 April 2007; revised 2 May 2007; accepted 10 May 2007
Available online 16 May 2007

Abstract—Two-step synthesis of 2-aryl-5-(phenylsulfanyl)furans was achieved starting from alkenyl aryl ketones and dichloromethyl phenyl sulfoxide. The phenylsulfanyl group was successfully converted to other functional groups, via sulfinyl group, to give highly substituted 2-arylfurans in good overall yields.

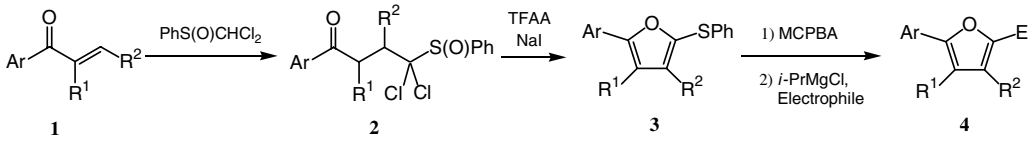
Furans are obviously one of the most important compounds in organic and synthetic organic chemistry. Furan moiety was frequently found as the skeletal structure of natural products, such as furano-terpenes, in the plant kingdom.[1] Furan is a relatively highly reactive heteroaromatic compound and is frequently used as an intermediate in organic synthesis.[2] In view of the importance of furans in organic chemistry many procedures for their synthesis have been reported;[3] however, new methods for their synthesis are still very much desired.

Over this decade, we have been interested in the development of new synthetic methods utilizing sulfoxides having a chlorinated alkyl group as a ligand.[4] As an extension of this study, we recently investigated for developing a new synthetic method using dichloromethyl phenyl sulfoxide, and a new procedure for a short synthesis of highly substituted furans was achieved (Scheme 1).

The essence of the procedure presented in this Letter is as follows. Thus, conjugate addition of the lithium carbanion of dichloromethyl phenyl sulfoxide to alkenyl aryl ketones **1** gave adduct **2** in high yield. The adduct was treated with trifluoroacetic anhydride (TFAA) in the presence of sodium iodide to give 2-aryl-5-(phenylsulfanyl)furan **3** in good yield. As the synthetic method for 2-thio-substituted furans is quite limited,[5] this is a good procedure for the synthesis from alkenyl aryl ketones **1** in only two steps.

The phenylsulfanyl group was oxidized to give a sulfoxide, which was treated with isopropylmagnesium chloride to afford 2-magnesiofuran via sulfoxide–magnesium exchange reaction. Finally the 2-magnesiofuran was treated with electrophiles to afford tri- or tetra-substituted furans **4** in good overall yield.

Details of this procedure are reported using 1-phenyl-2-buten-1-one **5** as an example (Scheme 2). To a solution of lithium carbanion of dichloromethyl phenyl sulfoxide[6] in THF in the presence of HMPA at −78 °C was added a solution of **5** in THF and the reaction mixture was stirred for 2 h to give adduct **6** in quantitative yield

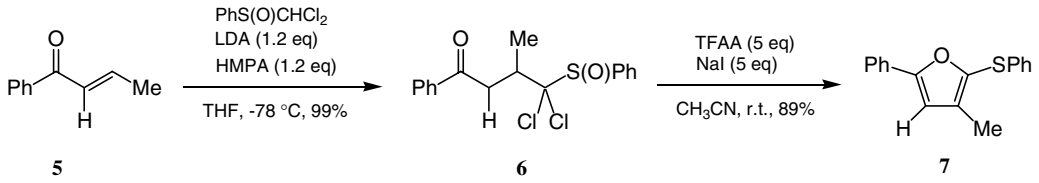


1 **2** **3** **4**

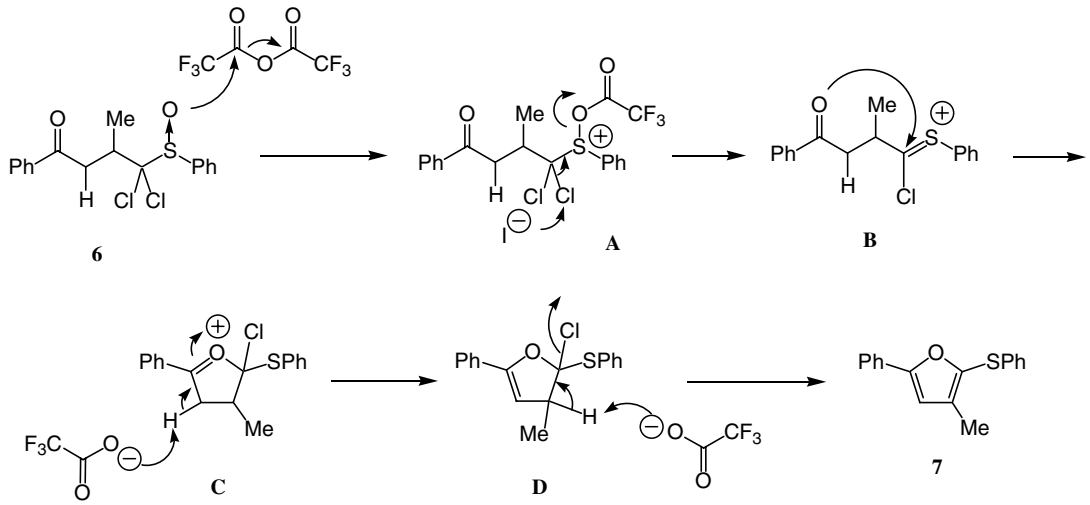
Scheme 1.

Keywords: Furan; Dichloromethyl phenyl sulfoxide; Pummerer reaction: 2-(Phenylsulfanyl)furan; Sulfoxide–magnesium exchange reaction.
* Corresponding author. E-mail: tsatoh@rs.kagu.tus.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.049



Scheme 2.



Scheme 3. A plausible mechanism for the reaction of **6** with TFAA–NaI giving furan **7**.

as a mixture of two diastereomers.[7,8] Adduct **6** was then treated with 5 equiv of TFAA in acetonitrile in the presence of 5 equiv of NaI at room temperature overnight. The starting material disappeared and from this rather clean reaction mixture, 4-methyl-2-phenyl-5-(phenylsulfanyl)furan **7** was obtained in 89% yield.[9]

The mechanism of this reaction is thought to be the Pummerer-type reaction[10] which is as follows (Scheme 3). At first, the reaction of sulfoxide **6** with TFAA gives an acyloxysulfonium ion **A**. The iodide anion attacks the chlorine atom to afford thionium ion **B**. The thionium ion is attacked by the oxygen atom of the carbonyl group[5d] to give cyclic oxonium ion **C**, from which the hydrogen at the β-position is picked up by the trifluoroacetate anion to afford dihydrofuran derivative **D**. As the elimination of HCl from intermediate **D** gives the aromatic compound, it would take place easily to give furan **7**.

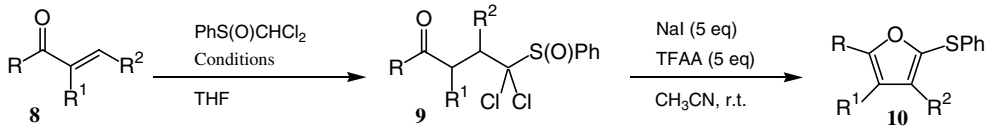
In order to investigate the generality of this reaction, first, the conjugate addition of lithium α-sulfinyl carbanion of dichloromethyl phenyl sulfoxide and several α,β-unsaturated carbonyl compounds was carried out, and second, the adducts were treated with TFAA–NaI as mentioned above. The results are summarized in Table 1.

The conjugate addition of all the investigated α,β-unsaturated carbonyl compounds gave adducts **9** in high to quantitative yields. Sodium hydride was found to be a better base for the addition reaction of α,β-unsaturated ester and amide (entries 8 and 9). Treatment of adduct **9** with TFAA–NaI was carried out under the same conditions as described above and the results are summarized in Table 1. Interestingly, the adducts derived from alkenyl aryl ketones gave the desired furans **10** in good yields except two examples (entries 1–6). When the adduct has alkyl group (methyl group) as R, entry 7, the reaction did not give the desired furan. The adducts derived from α,β-unsaturated ester and amide (entries 8 and 9) also did not give the expected furans but gave a complex mixture. From these results, the enolizability of ketone **9** (the acidity of the hydrogen at the α-position)[11] is thought to be quite important in this furan synthesis.

Table 2 shows the results for the synthesis of tri- and tetra-substituted furans **13** starting from several alkenyl phenyl ketones **11** via adducts **12**. As shown in the table, all adducts **12** were obtained under the same conditions as described above in 62–99% yields. The formation of furans **13** proceeded in good to excellent yields except one example (entry 3). In this case, the starting material did not disappear under the reaction conditions, and 58% yield of the starting material was recovered.

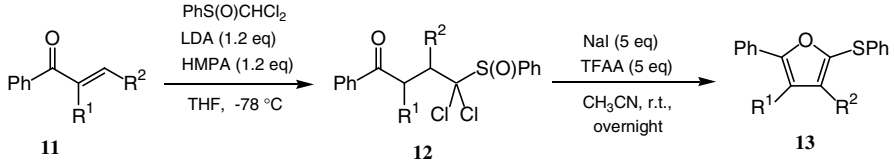
The phenylsulfanyl group in the produced furans could be used for further introducing functional groups. Thus, sulfoxide–metal exchange reaction[12] of the corresponding 2-sulfinylfuran would afford the corresponding 2-lithio- or 2-magnesiofuran, which could be trapped with several electrophiles to afford new furan derivatives. We investigated this idea and the preliminary results are summarized in Table 3.

Table 1. Synthesis of 2-(phenylsulfanyl)furans **10** from enones **8** through the adducts **9**



Entry	8			Conditions	Yield (%)	
	R	R^1	R^2		**9**	**10**
1	Phenyl	H	Me	LDA, HMPA (1.2 equiv), −78 °C	99	89
2	1-Naphthyl	H	Me		70	83
3	*p*-Methoxyphenyl	H	Me		99	25
4	*p*-Tolyl	H	Me		94	51
5	*p*-Fluorophenyl	H	Me		99	71
6	2-Thienyl	H	Me		92	36
7	Me	Me	Me		90	Complex mixture
8	*t*-BuO	H	H	NaH (2 equiv), 0 °C to rt	94	Complex mixture
9	Me_2N	H	H		99	Complex mixture

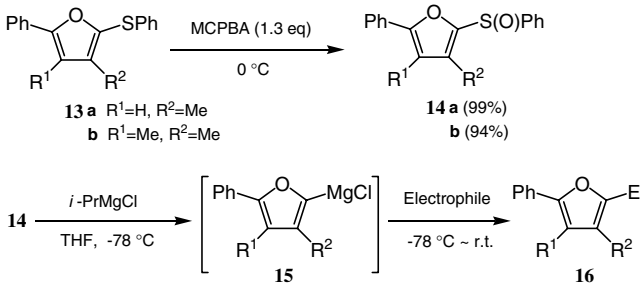
Table 2. Synthesis of 2-phenyl-5-(phenylsulfanyl)furans **13** from enones **11** through the adducts **12**



Entry	11		Yield (%)	
	R^1	R^2	**12**	**13**
1	H	*n*-Pr	93	88
2	H	*i*-Pr	72	83
3	H	Ph	62	41[a]
4	Me	H	99	61
5	Me	Me	91	72
6	Me	*n*-Pr	91	99

[a] Starting material was recovered in 58%.

Table 3. Synthesis of tri- and tetra-substituted furans **16** from 2-phenyl-5-(phenylsulfanyl)furans **13** via 2-magnesiofurans **15** derived from sulfoxides **14** with *i*-PrMgCl



Entry	R^1	R^2	*i*-PrMgCl (equiv)	Electrophile (equiv)		Yield (%) **16**	
1	H	Me	1.8	CH_3OH	Excess	88	(E = H)
2	H	Me	1.8	ClCOOEt	3.0	59	(E = COOEt)
3	H	Me	1.8	ClCOPh	3.0	69	(E = COPh)
4	Me	Me	3.0	ClCOOEt	5.0	63	(E = COOEt)
5	Me	Me	3.0	ClCOPh	5.0	57	(E = COPh)

At first, furans **13a** and **13b** were oxidized to the corresponding sulfoxides **14a** and **14b**, respectively, in almost quantitative yields. Sulfoxide **14a** was treated with 1.8 equiv of isopropylmagnesium chloride in THF at −78 °C (2-magnesiofuran intermediate **15** was generated) and the reaction was quenched with methanol to afford 4-methyl-2-phenylfuran (Table 3, entry 1) in 88% yield. The intermediate was treated with ethyl

chloroformate and benzoyl chloride to give ethoxycarbonylated and benzoylated furans, respectively (entries 2 and 3), in moderate to good yields.[13] A similar treatment of **14b** gave tetra-substituted furans (entries 4 and 5) in about 60% yield.

In conclusion, we have developed a new synthetic method for 2-aryl-5-(phenylsulfanyl)furans from alkenyl aryl ketones with dichloromethyl phenyl sulfoxide in only two steps. By utilization of the sulfanyl group, the synthesis of fully substituted 2-arylfurans was also achieved. The procedure presented in this Letter will contribute to the synthesis of highly substituted furans.

References and notes

1. (a) *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed. Stereoselective Synthesis (Part D); Elsevier: Amsterdam, 1990; Vol. 6, pp 107–132; (b) Jefford, C. W.; Sledeski, A. W.; Rossier, J.-C.; Boukouvalas, J. *Tetrahedron Lett.* **1990**, *31*, 5741; (c) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450; (d) Aso, M.; Ojida, A.; Yang, G.; Cha, O.-J.; Osawa, E.; Kanematsu, K. *J. Org. Chem.* **1993**, *58*, 3960.
2. Reviews and selected recent papers for furans as intermediates in organic synthesis: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795; (b) Tsubuki, M. *J. Syn. Org. Chem. Jpn.* **1993**, *51*, 399; (c) Griffith, G. A.; Hillier, I. H.; Moralee, A. C.; Percy, J. M.; Roig, R.; Vincent, M. A. *J. Am. Chem. Soc.* **2006**, *128*, 13130; (d) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.
3. Recent reviews and papers for synthesis of furans: (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850; (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076; (c) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *x*, 121; (d) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769; (e) Tseng, J.-C.; Chen, J.-H.; Luh, T.-Y. *Synlett* **2006**, 1209; (f) Sniady, A.; Durham, A.; Morreale, M. S.; Wheele, K. A.; Dembinski, R. *Org. Lett.* **2007**, *9*, 1175.
4. Some of our new recent synthetic methods utilizing chloromethyl *p*-tolyl sulfoxide and 1-chloroalkyl aryl sulfoxides: (a) Satoh, T.; Osawa, A.; Ohbayashi, T.; Kondo, A. *Tetrahedron* **2006**, *62*, 7892; (b) Satoh, T.; Hirano, M.; Kuroiwa, A.; Kaneko, Y. *Tetrahedron* **2006**, *62*, 9268; (c) Satoh, T.; Tanaka, S.; Asakawa, N. *Tetrahedron Lett.* **2006**, *47*, 6769; (d) Satoh, T.; Ogata, S.; Wakasugi, D. *Tetrahedron Lett.* **2006**, *47*, 7249; (e) Satoh, T.; Sugiyama, S. *J. Syn. Org. Chem. Jpn.* **2006**, *64*, 1049; (f) Satoh, T.; Takahashi, Y.; Shirai, Y.; Yamada, Y. *Chem. Pharm. Bull.* **2006**, *54*, 1734; (g) Sugiyama, S.; Shimizu, H.; Satoh, T. *Tetrahedron Lett.* **2006**, *47*, 8771; (h) Fukushima, I.; Gouda, Y.; Satoh, T. *Tetrahedron Lett.* **2007**, *48*, 1855; (i) Sakurada, J.; Satoh, T. *Tetrahedron* **2007**, *63*, 3806; (j) Kashima, H.; Kawashima, T.; Wakasugi, D.; Satoh, T. *Tetrahedron* **2007**, *63*, 3953.
5. (a) Nolan, S. M.; Cohen, T. *J. Org. Chem.* **1981**, *46*, 2473; (b) Datta, A.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetrahedron* **1989**, *45*, 7631; (c) Padwa, A.; Ginn, J. D.; McClure, M. S. *Org. Lett.* **1999**, *1*, 1559; (d) Sarkar, T.; Panda, N.; Basak, S. *J. Org. Chem.* **2003**, *68*, 6919.
6. Dichloromethyl phenyl sulfoxide was reported to be synthesized from methyl phenyl sulfoxide in two steps in 60% overall yield by Durst (Tin, K.-C.; Durst, T. *Tetrahedron Lett.* **1970**, 4643). We reinvestigated the synthesis of dichloromethyl phenyl sulfoxide as follows. Recrystallized *N*-chlorosuccinimide (27.4 g; 0.205 mol) was added to a solution of methyl phenyl sulfoxide (14.0 g; 0.1 mol) in 200 mL of THF at 0 °C with stirring. The reaction mixture was stirred at room temperature overnight. The precipitate was filtered off and the solvent of the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography to give dichloromethyl phenyl sulfoxide (19.8 g; 95%) as a colorless oil.
7. Mahidol, C.; Reutrakul, V.; Panyachotipun, C.; Turongsomboon, G.; Prapansiri, V.; Bandara, B. M. R. *Chem. Lett.* **1989**, 163.
8. HMPA (1.86 mL; 10.4 mmol) was added to a solution of LDA (10.4 mmol) in 39 mL of dry THF at −78 °C with stirring. After the solution was stirred for 10 min, a solution of dichloromethyl phenyl sulfoxide (1.81 g; 8.67 mmol) in 2 mL of dry THF was added and the reaction mixture was stirred for 10 min. To this solution of carbanion, a solution of **5** (1.65 g; 11.3 mmol) in 2 mL of dry THF was added. The reaction mixture was stirred for 2 h, then the reaction was quenched by satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give 4-benzenesulfinyl-4,4-dichloro-3-methyl-1-phenylbutan-1-one **6** (3.05 g; 99%) as colorless crystals (about 1:1 diastereomeric mixture). IR (diastereomeric mixture; KBr) 2980, 1685 (CO), 1447, 1354, 1277, 1091, 752 cm^{-1}; ^1H NMR (less polar product) δ 1.40 (3H, d, $J = 6.5$ Hz), 3.16 (1H, dd, $J = 17.0$, 10.0 Hz), 3.34–3.42 (1H, m), 3.80 (1H, dd, $J = 17.0$, 1.2 Hz), 7.49 (2H, t, $J = 7.3$ Hz), 7.53–7.65 (4H, m) 7.86 (2H, t, $J = 7.1$ Hz), 8.02 (2H, d, $J = 7.1$ Hz); (more polar product) δ 1.43 (3H, d, $J = 6.2$ Hz), 3.16 (1H, dd, $J = 17.0$, 10 Hz), 3.48–3.56 (1H, m), 3.70 (1H, dd, $J = 17.0$, 1.8 Hz), 7.48 (2H, t, $J = 7.8$ Hz), 7.53–7.64 (4H, m), 7.87 (2H, t, $J = 7.1$ Hz), 8.00 (2H, d, $J = 7.0$ Hz). MS (diastereomeric mixture) *m*/*z* (%) 266 (M^+, 100), 189 (8), 161 (18), 105 (43), 77 (22). Anal. Calcd for $C_{17}H_{14}OS$: M, 266.0760. Found: *m*/*z* 266.0763.
9. TFAA (0.139 mL; 1.0 mmol) was added to a solution of **6** (71.1 mg; 0.2 mmol) and NaI (150 mg; 1.0 mmol) in acetonitrile (2 mL) at room temperature with stirring. The solution was stirred overnight, then the reaction was quenched by satd aq $NaHCO_3$ and satd aq Na_2SO_3. The whole was extracted with CH_2Cl_2. The product was purified by silica gel column chromatography to give 3-methyl-5-phenyl-2-(phenylsulfanyl)furan **7** (47.3 mg; 89%) as colorless crystals. Mp 36.0–36.5 °C (hexane). IR (KBr) 3061, 1581, 1487, 1024, 928, 761 cm^{-1}; ^1H NMR δ 2.16 (3H, s), 6.66 (1H, s), 7.11–7.15 (3H, m), 7.21–7.28 (3H, m), 7.36 (2H, t, $J = 7.8$ Hz), 7.67 (2H, d, $J = 7.2$ Hz). ^{13}C NMR δ 156.40 (C), 138.55 (C), 137.14 (C), 131.59 (C), 130.26 (C), 129.05 (CH), 128.68 (CH), 127.95 (CH), 126.64 (CH), 125.86 (CH), 124.05 (CH), 108.97 (CH), 11.20 (CH_3). MS *m*/*z* (%) 266 (M^+, 100), 189 (8), 161 (18), 105 (43), 77 (22). Anal. Calcd for $C_{17}H_{14}OS$: M, 266.0760. Found: *m*/*z* 266.0763.
10. (a) Padwa, A.; Gunn, D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353; (b) Satoh, T.; Sugiyama, S.; Ota, H. *Tetrahedron Lett.* **2002**, *43*, 3033; (c) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003.
11. The value of pK_a of the α-hydrogen of aryl ketones was reported to be 24–26 (Bordwell, F. G.; Cornforth, F. J. *J. Org. Chem.* **1978**, *43*, 1763). While that of alkyl ketones and esters was reported to be 27–30 ((a) Zhang, X. M.; Bordwell, F. G.; Puy, M. V. D.; Fried, H. E. *J. Org. Chem.* **1993**, *58*, 3060. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456). Obviously, aryl ketones are prone to be enolized easier than alkyl ketones.

12. (a) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H.; Oae, S. *Tetrahedron Lett.* **1986**, *27*, 3899; (b) Satoh, T.; Matsue, R.; Fujii, T.; Morikawa, S. *Tetrahedron* **2001**, *57*, 3891; (c) Akai, S.; Kawashita, N.; Satoh, H.; Wada, Y.; Kakiguchi, K.; Kuriwaki, I.; Kita, Y. *Org. Lett.* **2004**, *6*, 3793.

13. To a solution of **14a** (56.5 mg ; 0.2 mmol) in 2 mL of dry THF at −78 °C was added *i*-PrMgCl (2.0 M solution in THF, 0.18 mL; 0.36 mmol) dropwise to give instantaneously 2-magnesiofuran **15a**. Ethyl chloroformate (0.057 mL; 0.60 mmol) was added to the reaction mixture and the mixture was gradually allowed to warm to room temperature. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give methyl 3-methyl-5-phenylfuran-2-carboxylate **16a** (27.3 mg; 59%) as colorless crystals. Mp 73.0–73.5 °C (hexane). IR (KBr) 2980, 1704 (CO), 1294, 1170, 930, 767 cm^{-1}; ^1H NMR δ 1.41 (3H, t, $J = 7.2$ Hz), 2.39 (1H, s), 4.38 (2H, q, $J = 7.2$ Hz), 6.60 (1H, s), 7.30 (1H, t, $J = 7.2$ Hz), 7.40 (2H, t, $J = 7.2$ Hz), 7.75 (2H, d, $J = 7.2$ Hz). ^{13}C NMR δ 179.23, 175.09, 159.05, 152.30, 149.05, 148.19, 144.25, 129.64, 79.91, 33.90, 31.29. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.12; H, 6.07.