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SYNTHESIS AND REACTIONS OF 5-ARYL-2-THIOPHENECARB-ALDEHYDES*

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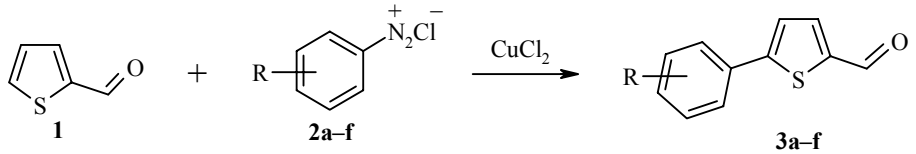
The reaction of 2-thiophenecarbaldehyde with arene diazonium chlorides in the presence of $CuCl_2$ catalyst gave 5-aryl-2-thiophenecarbaldehydes. Use of 4-nitrobenzene diazonium chloride in the reaction also gave the isomeric 3-(4-nitrophenyl)-2-thiophenecarbaldehyde. Condensation products of the 5-aryl-2-thiophenecarbaldehydes with cyanoacetic acid esters, cyanoacetamide, and with barbituric and dimethylbarbituric acids were prepared.

Keywords: 5-aryl-2-thiophenecarbaldehydes, 2-thiophenecarbaldehyde, arylation, Meerwein reaction.

The copper-catalyzed reaction of arene diazonium salts with unsaturated compounds (the Meerwein reaction) is a convenient method for the preparation of polyfunctional compounds [2-4]. Heteroaromatic compounds occupy a special place amongst unsaturated substrates which have been used in this reaction. Several furan derivatives (particularly furfural) have been well studied in arylation reactions with diazonium salts since they proved to be most reactive [4-7]. The arylfuran compounds obtained have found use as reagents for introducing 2-arylfuran fragments in the synthesis of practically useful substances (e.g. see [8, 9]).

5-Aryl-2-thiophenecarbaldehydes have also found widespread use as reagents [10-13]. They are usually prepared by formylation of arylthiophenes [10] or by palladium-catalyzed arylation of 2-thiophenecarbaldehyde by various reagents [11-15]. It should be noted that the reactions are not always selective in the latter case [16].

As seen in literature data [17-19], under Meerwein reaction conditions 2-thiophenecarbaldehyde is arylated in low yields. At the same time this method is preparatively most attractive since it does not involve hard to obtain starting compounds and catalysts.



2, 3 a R = 4-NO_2, **b** R = 3-NO_2, **c** R = 4-Cl, **d** R = 2,4-Cl_2, **e** R = 2,5-Cl_2, **f** R = $SCHF_2$

* Communication 16 in the series "Synthesis of heterocycles based on the products of arylation of unsaturated compounds". For Communication 15 see [1].

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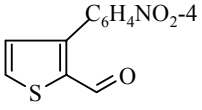
For this reason we have carried out a more detailed study of the arylation of 2-thiophenecarbaldehyde **1** by the arene diazonium chlorides **2a-f**. The reaction takes place in the presence of $CuCl_2$ catalyst at room temperature to give the 5-aryl-2-thiophenecarbaldehydes **3a-f** (Tables 1 and 2).

The reaction was performed in an aqueous–organic medium. Acetone, acetonitrile, DMF, and DMSO were used as the organic solvent. Compounds **3a-f** were obtained with the highest yields (greater than in [17-19]) using DMSO. It should be stressed that the Meerwein reaction is associated with moderate yields (30-40%) [4]. The aldehyde **1** reacts most vigorously with 4-nitrobenzene diazonium chloride. However, in this case, it was found that an isomeric 3-(4-nitrophenyl)-2-thiophenecarbaldehyde (**4**) is formed together with compound **3a** (overall yield 77%). In the ^{1}H NMR spectrum of compound **4** (Table 2) the thiophene ring protons appear as two doublets, one of which is shifted to low field.



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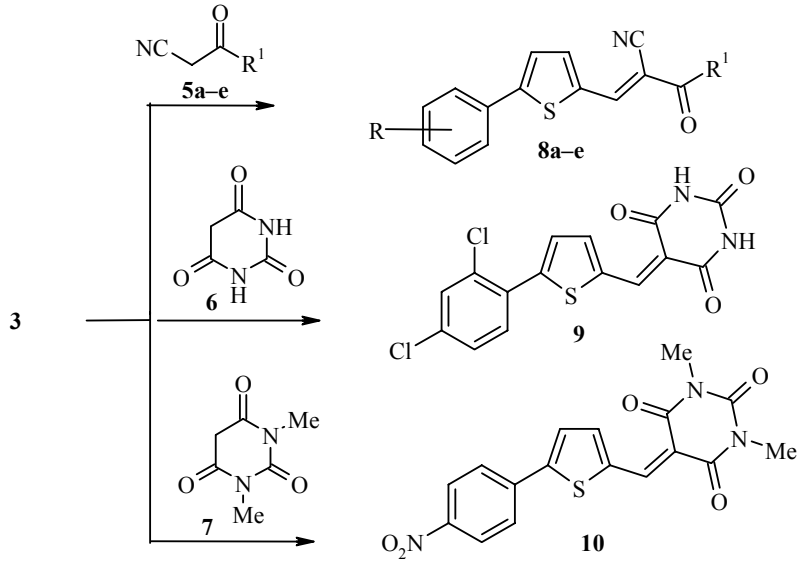
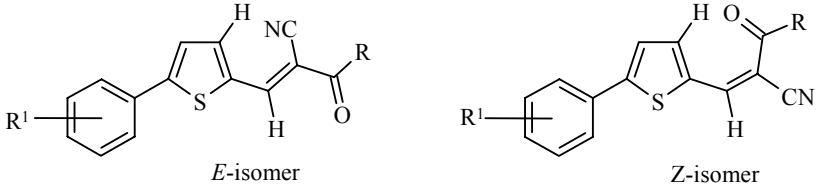
As already mentioned, the 5-aryl-2-thiophenecarbaldehydes **3a-f** are promising reagents for organic synthesis. We have studied their reaction with several active methylene compounds. It was found that they readily condense with the cyanoacetic acid esters **5a-d**, cyanoacetamide (**5e**), and with barbituric (**6**) and dimethylbarbituric acids **7** to give compounds **8-10** (Table 1).



8 a R = 4-Cl, R^1 = OMe, **b** R = 2,4-Cl_2, R^1 = OMe, **c** R = 2,4-Cl_2, R^1 = OEt,
d R = 2,4-Cl_2, R^1 = OBu, **e** R = 4-Cl, R^1 = NH_2

Compounds **8a-e** can exist as *Z*- and *E*-isomers. In addition the thiophene ring and the exocyclic double bond can take an *s-cis*- or *s-trans* configuration as discussed for similar furan series compounds in the studies [6, 20, 21].



E-isomer Z-isomer

TABLE 1. Characteristics of the Compounds **3a,d-f, 4, 8a-e, 9, 10**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield %
		C	H	N	S		
3a,4 mixture	$C_{11}H_7NO_3S$	56.32 / 56.64	2.96 / 3.03	6.12 / 6.01	13.59 / 13.75	—	50 (**3a**), 27 (**4**)
3d	$C_{11}H_6Cl_2OS$	51.28 / 51.38	2.26 / 2.35		12.33 / 12.47	112-113	42
3e	$C_{11}H_6Cl_2OS$	51.43 / 51.38	2.14 / 2.35		12.52 / 12.47	103-104	31
3f	$C_{12}H_8F_2OS_2$	53.43 / 53.32	2.75 / 2.98		23.66 / 23.72	57-58	36
8a	$C_{15}H_{10}ClNO_2S$	59.60 / 59.31	3.10 / 3.32	4.45 / 4.61	10.39 / 10.56	160-161	40
8b	$C_{15}H_9Cl_2NO_2S$	53.13 / 53.27	2.54 / 2.68	4.25 / 4.14	9.40 / 9.48	174-175	45
8c	$C_{16}H_{11}Cl_2NO_2S$	54.38 / 54.56	3.01 / 3.15	4.05 / 3.98	8.89 / 9.10	150-152	55
8d	$C_{18}H_{15}Cl_2NO_2S$	56.64 / 56.85	3.84 / 3.98	3.87 / 3.68	8.40 / 8.43	108-109	59
8e	$C_{14}H_9ClN_2OS$	58.17 / 58.23	2.91 / 3.14	9.59 / 9.70	11.01 / 11.10	242-243	70
9	$C_{15}H_8Cl_2N_2O_3S$	48.87 / 49.06	2.06 / 2.20	7.59 / 7.63	8.61 / 8.73	>300	35
10	$C_{17}H_{13}N_3O_5S$	54.87 / 54.98	3.76 / 3.53	11.19 / 11.31	8.69 / 8.63	319-320	30

As is evident from the ^{1}H NMR spectra (Table 2), compounds **8a,c,e** are formed as a mixture of *Z*- and *E*-isomers but **8b,d** have an *E*-configuration The alkoxycarbonyl or amide group (RCO) deshields the proton situated in a *cis*-position to it more strongly than does the CN group.

TABLE 2. ^{1}H NMR Spectra of Compounds **3, 4, 8-10**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
3a	7.80-7.89 (2H, m, thiophene); 9.95 (1H, s, CHO)
4	7.42 (1H, d, *J* = 4.5, H-4 thiophene); 8.12 (1H, d, *J* = 4.5, H-5 thiophene); 9.84 (1H, s, CHO)
3a+4	8.02-8.07 (2H, m, C_6H_4); 8.27-8.35 (2H, m, C_6H_4)
3d	7.47 (1H, dd, *J* = 2.2 and *J* = 8.4, H-5 C_6H_3); 7.56 (1H, d, *J* = 3.8, H-4 thiophene); 7.65 (1H, d, *J* = 2.2, H-3 C_6H_3); 7.69 (1H, d, *J* = 8.4, H-6 C_6H_3); 7.98 (1H, d, *J* = 3.8, H-3 thiophene); 9.94 (1H, s, CHO)
3e	7.44 (1H, d, *J* = 8.2, H-3 C_6H_3); 7.49 (1H, d, *J* = 3.8, H-4 thiophene); 7.63-7.67 (1H, m, H-4 C_6H_3); 7.94 (1H, d, *J* = 3.8, H-3 thiophene); 8.03 (1H, d, *J* = 2.0, H-6 C_6H_3); 9.96 (1H, s, CHO)
3f	7.44 (1H, t, J_{HF} = 56, CHF_2); 7.53 (1H, d, *J* = 3.8, H-4 thiophene); 7.55 (2H, d, *J* = 8.0, C_6H_4); 7.76 (2H, d, *J* = 8.0, C_6H_4); 7.84 (1H, d, *J* = 3.8, H-3 thiophene); 9.95 (1H, s, CHO)
8a	3.83 (1.5H, s, OCH_3); 3.87 (1.5H, s, OCH_3); 7.37-7.58 (3.5H, m, C_6H_4+H-4 thiophene, *Z*-isomer); 7.69 (0.5H, d, *J* = 4.8, H-4 thiophene, *E*-isomer); 7.78 (1H, d, *J* = 8.8, C_6H_4); 8.00 (0.5H, d, *J* = 3.5, H-3 thiophene, *E*-isomer); 8.18 (0.5H, d, *J* = 4.8, H-3 thiophene, *Z*-isomer); 8.19 (0.5H, s, =CH, *Z*-isomer); 8.51 (0.5H, s, =CH, *E*-isomer)
8b	3.88 (3H, s, OCH_3); 7.49 (1H, dd, *J* = 1.8 and *J* = 8.0, H-5 C_6H_3); 7.61 (1H, d, *J* = 4.0, H-4 thiophene); 7.66 (1H, d, *J* = 1.8, H-3 C_6H_3); 7.73 (1H, d, *J* = 8.0, H-6 C_6H_3); 8.04 (1H, d, *J* = 4.0, H-3 thiophene); 8.56 (1H, s, CH)

TABLE 2 (continued)

1	2
8c	1.32 t and 1.36 t (3H, *J* = 6.8, CH_3); 4.24-4.39 (2H, m, OCH_2); 7.36-7.59 (2.4H, m, C_6H_3 + H-4 thiophene, *Z*-isomer); 7.68 (0.6H, d, *J* = 3.5, H-4 thiophene, *E*-isomer); 7.78 (2H, d, *J* = 9.0, C_6H_3); 7.99 (0.6H, d, *J* = 3.5, H-3 thiophene, *E*-isomer); 8.17 (0.4H, d, *J* = 4.8, H-3 thiophene, *Z*-isomer); 8.20 (0.4H, s, =CH, *Z*-isomer); 8.49 (0.6H, s,=CH, *E*-isomer)
8d	0.98 (3H, t, *J* = 7.0, CH_3); 1.40-1.51 (2H, m, $C\underline{H_2}CH_3$); 1.65-1.76 (2H, m, $CH_2C\underline{H_2}CH_2$); 4.27 (2H, t, *J* = 6.5, OCH_2); 7.49 (1H, d, *J* = 8.5, H-5 C_6H_3); 7.60 (1H, d, *J* = 4.0, H-4 thiophene); 7.67 (1H, s, H-3 C_6H_3); 7.73 (1H, d, *J* = 8.5, H-6 C_6H_3); 8.04 (1H, d, *J* = 4.0, H-3 thiophene); 8.52 (1H, s, =CH)
8e	7.32 (0.5H, d, *J* = 4.8, H-4 thiophene, *Z*-isomer); 7.38-7.59 (4H, m, C_6H_4 + NH_2); 7.63 (0.5H, d, *J* = 3.8, H-4 thiophene, *E*-isomer); 7.75 (2H, d, *J* = 7.8, C_6H_4); 7.81 (0.5H, d, *J* = 3.8, H-3 thiophene, *E*-isomer); 8.03 (0.5H, d, *J* = 4.8, H-3 thiophene, *Z*-isomer); 8.11 (0.5H, s, =CH, *Z*-isomer); 8.32 (0.5H, s, CH, *E*-isomer)
9	7.48 (1H, dd, *J* = 2.0 and *J* = 8.7, H-5 C_6H_3); 7.58 (1H, d, *J* = 3.8, H-4 thiophene); 7.65 (1H, d, *J* = 2.0, H-3 C_6H_3); 7.71 (1H, d, *J* = 8.7, H-6 C_6H_3); 8.10 (1H, d, *J* = 3.8, H-3 thiophene); 8.52 (1H, s, =CH); 11.22 (2H, s, NH)
10	3.33 (3H, s, NCH_3); 3.35 (3H, s, NCH_3); 7.88 (1H, d, *J* = 3.8, H-4 thiophene); 8.09 (2H, d, *J* = 8.0, C_6H_4); 8.13 (1H, d, *J* = 3.8, H-3 thiophene); 8.31 (2H, d, *J* = 8.0, C_6H_4); 8.62 (1H, s, =CH)

For the *E*-isomer such an effect corresponds to the shift to low field of the proton signal of the exocyclic bond (CH=). For the *Z*-isomer the proton signal at position 3 of the thiophene ring is shifted to low field and this is specifically caused by the *s-cis* configuration. According to the intensities of the corresponding signals the ratio of *E*- to *Z*-isomers is: **8a,e** ~50:50, **8c** 60:40.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250 MHz) using DMSO-d_6 using HMDS (δ 0.05 ppm) as internal standard. Mass spectra were obtained on a Finnigan MAT INKOS-50 chromato-mass spectrometer with ionization energy of 70 eV.

5-Arylthiophene-2-carbaldehydes 3a-f (General Method). A solution of $NaNO_2$ (7 g) in water (25 ml) was added dropwise with stirring to a solution of the aromatic amine (0.1 mol) in 20% HCl (60 ml) cooled to 0-5ºC. The solution of arene diazonium salt **2a-f** obtained was filtered and added dropwise with stirring to a mixture of the aldehyde **1** (15 ml, 12.25 g, 0.11 mol), DMSO (40 ml), and $CuCl_2 \cdot 2H_2O$ (1.5 g, 8.7 mmol). The reaction was carried out at 15-25ºC in such a manner that the nitrogen was evolved at a moderate rate. Water (150 ml) was added to the reaction mixture after nitrogen evolution had ceased. The precipitate formed was recrystallized from a mixture of ethanol and DMF. The ratio of aldehydes **3a** to **4** in the precipitate formed after carrying out the reaction was about 2:1 according to ^{1}H NMR. An analytically pure sample of aldehyde mixture was recrystallized from a mixture of ethanol and DMF.

5-(3-Nitrophenyl)-2-thiophenecarbaldehyde (3b) was obtained in 28% yield; mp 144-145ºC ([22], mp 147ºC) and **5-(4-chlorophenyl)-2-thiophenecarbaldehyde (3c)** in 27% yield; mp 88-89ºC ([23], mp 89-90ºC).

The characteristics of the remaining aldehydes are given in Tables 1 and 2.

3-(5-Aryl-2-thienyl)-2-cyanopropenoate Esters 8a-d. The aldehyde **3** (50 mmol) and ethyl cyanoacetate (50 mmol) were dissolved in ethanol (20 ml), several drops of pyridine were added, and the product was refluxed for 0.5-1.5 h. The precipitate formed was filtered off, washed with ethanol, and recrystallized from benzene. Compound **8e** was prepared similarly from cyanoacetamide.

5-[5-(2,4-Dichlorophenyl)-2-thienylmethylene]hexahydropyrimidine-2,4,6-trione (9). The aldehyde **3d** (2.58 g, 10 mmol) and barbituric acid **6** (1.28 g, 10 mmol) were dissolved in acetic acid (30 ml), several drops of pyridine added, and the product was refluxed for 1 h. The precipitate formed was filtered off, washed with ethanol, and recrystallized from ethanol.

1,3-Dimethyl-5-[5-(4-nitrophenyl)-2-thienylmethylene]hexahydropyrimidine-2,4,6-trione (10) was prepared similarly by treating the aldehyde **3a** with dimethylbarbituric acid **7**. Mass spectrum, *m/z* (I_{rel}, %): 371 (100), 257 (49), 171 (24), 139 (90).

REFERENCES

1. M. D. Obushak, V. V. Kaepyak, Y. V. Ostapiuk, and V. S. Matiychuk, *Phosph. Sulfur, Silicon Relat. Elem.*, **182**, 1437 (2007).
2. K. H. Saunders and R. L. Allen, *Aromatic Diazo compounds*, Edward Arnold, London (1985), p. 594.
3. H. Zollinger, *Diazo Chemistry. I. Aromatic and Heteroaromatic Compounds*, VCH, Weinheim (1994), p. 243.
4. C. S. Rondestvedt, in: *Organic Reactions*, Vol. 24, John Wiley, New York, London (1976), p. 225.
5. N. D. Obushak, A. I. Lesyuk, N. I. Ganuschak, G. M. Mel'nik, and Yu. P. Zavalii, *Zh. Org. Khim*, **22**, 2331 (1986).
6. N. D. Obushak, N. I. Ganuschak, A. I. Lesyuk, L. M. Dzikovskaya, and P. P. Kisilitsa, *Zh. Org. Khim.*, **26**, 873 (1990).
7. A. F. Oleinik, T. I. Vozyakova, G. A. Modnikova, and K. Yu. Novitskii, *Khim. Geterotsikl. Soedin.*, 441 (1972). [*Chem. Heterocycl. Comp.*, **8**, (1972)].
8. D. Balachari, L. Quinn, and G. A. O'Doherty, *Tetrahedron Lett.*, **40**, 4769 (1999).
9. S. Holla, R. Gonsalves, and S. Shenoy, *Eur. J. Med. Chem.*, **35**, 267 (2000).
10. T. Noguchi, M. Hasegawa, K. Tomisawa, and M. Mitsukuchi, *Bioorg. Med. Chem.*, **11**, 4729 (2003).
11. M. Michaelides, Y. Hong, S. DiDomenico, E. K. Bayburt, K. E. Asin, D. R. Britton, C. Wel Lin, and K. Shiosaki, *J. Med. Chem.*, **40**, 1585 (1997).
12. A. Tanaka, T. Terasawa, H. Hagihara, Y. Sakuma, N. Ishibe, M. Sawada, H. Takasugi, and H. Tanaka, *J. Med. Chem.*, **41**, 2390 (1998).
13. T. Hosoya, H. Aoyama, T. Ikemoto, Y. Kihara, T. Hiramatsu, M. Endo, and M. Suzuki, *Bioorg. Med. Chem.*, **11**, 663 (2003).
14. D. A. Alonso, C. Náera, and M. C. Pacheco, *J. Org. Chem.*, **67**, 5588 (2002).
15. T. E. Barder and S. L. Buchwald, *Org. Lett.*, **6**, 2649 (2004).
16. T. Itahara, *J. Org. Chem.*, **50**, 5272 (1985).
17. R. Frimm, L. Fišera, and J. Kovać, *Collect. Czech. Chem. Commun.*, **38**, 1809 (1973).
18. L. Racane, V. Tralić-Kulenović, D. W. Boykin, and G. Karminski-Zamola, *Molecules*, **8**, 342 (2003).
19. L. Racane, V. Tralić-Kulenović, G. Karminski-Zamola, and L. Fišer-Jakić, *Monatsh. Chem.*, **126**, 1375 (1995).
20. V. K. Kul'nevich, P. A. Pavlov, and G. D. Krapivin, *Khim. Geterotsikl. Soedin.*, 1169 (1986). [*Chem. Heterocycl. Comp.*, **22**, 943 (1986)].
21. S. Fisichella, G. Mineri, G. Scarlata, and D. Sciotto, *Tetrahedron*, **31**, 2445 (1975).
22. W. Hanefeld and M. Schlitzer, *J. Heterocycl. Chem.*, **32**, 1019 (1995).
23. C. M. Beaton, N. B. Chapman, K. Clarke, and J. M. Willis, *J. Chem. Soc., Perkin Trans. 1,* 2355 (1976).