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THREE-COMPONENT SYNTHESIS OF DIMETHYL 7-ARYL-8-(3-ARYLQUINOXALIN-2-YL)-2-(R-IMINO)-9-OXO-1,6-DIOXA-SPIRO[4.4]NONA-3,7-DIENE-3,4-DICARBOXYLATES

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We have developed a method for the synthesis of dimethyl 7-aryl-8-(3-arylquinoxalin-2-yl)-2-(R-imino)-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylates, based on a three-component reaction of 5-aryl-4-(quinoxalin-2-yl)furan-2,3-diones, 1-adamantylisocyanide or o-methylphenylisocyanide, and dimethyl acetylenedicarboxylate.

Keywords: 5-aryl-4-(quinoxalin-2-yl)furan-2,3-diones, dimethyl acetylenedicarboxylate, dimethyl 7-aryl-8-(3-arylquinoxalin-2-yl)-2-(R-imino)-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylates, isocyanides, methyl 2-[5-aryl-4-(quinoxalin-2-yl)-3-oxo-2(3*H*)-furanylidene]acetate, γ-spiroiminolactones, multicomponent reaction.

Multicomponent reactions (MCRs) are effective and accessible methods for the synthesis of organic compounds. The main advantage of this type of reactions is the large number of products that can be prepared in one stage from simple and easily available starting materials [1]. MCRs are widely used for many different practical applications: the discovery of biologically active compounds, catalysts, novel materials, etc. Such reactions generally provide good yields, are fast, and in most cases proceed under mild conditions. Major advances in this field have been achieved by using isocyanides, the unique properties of which have enabled the development of remarkably effective approaches to the synthesis of complex organic compounds [2-4]. A three-component synthesis based on isocyanides, carbonyl compounds, and acetylenedicarboxylic esters is an example of successful MCR, which has been recently used for the synthesis of diverse heterocyclic compounds [5]. This reaction has provided access to substituted furans [6-7], pyrroles [8], pyrans [9-10], and other heterocyclic systems, which were difficult or impossible to prepare by other methods. Only one case has been reported in the literature, where a similar reaction was performed with furan-2,3-diones in the role of the carbonyl component [11].

We used a three-component reaction of 5-aryl-4-(quinoxalin-2-yl)furan-2,3-diones **1a-c** [12], dimethyl acetylenedicarboxylate, and 1-adamantylisocyanide or *o*-methylphenylisocyanide [13] to obtain high yields of the dimethyl 7-aryl-8-(3-arylquinoxalin-2-yl)-2-(R-imino)-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylates **2a-f** as the only products (Table 1).

The spirocompounds **2a-f** are yellow or colorless crystals with high melting points, readily soluble in chloroform, poorly soluble in acetonitrile and alcohol, insoluble in water and alkanes.

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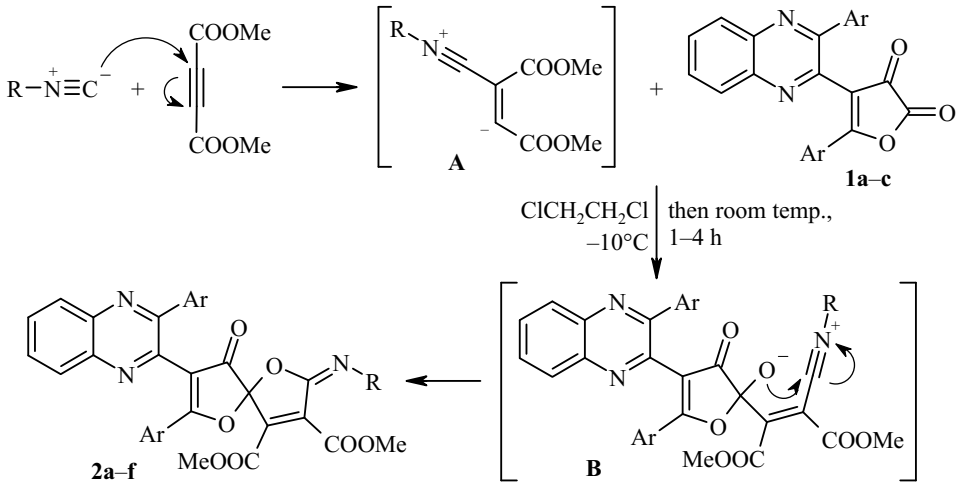
TABLE 1. Physicochemical Characteristics of the Synthesized Compounds **2a-f** and **3a-c**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
2a	$C_{41}H_{35}N_3O_7$	72.36 / 72.23	5.24 / 5.17	6.26 / 6.16	269-270	87
2b	$C_{43}H_{39}N_3O_7$	72.63 / 72.76	5.41 / 5.54	5.99 / 5.92	286-287	85
2c	$C_{45}H_{43}N_3O_7$	73.32 / 73.25	5.77 / 5.87	5.79 / 5.69	203-205	89
2d	$C_{38}H_{27}N_3O_7$	71.50 / 71.58	4.35 / 4.27	6.66 / 6.59	145-147	84
2e	$C_{40}H_{31}N_3O_7$	72.21 / 72.17	4.78 / 4.69	6.23 / 6.31	190-191	86
2f	$C_{42}H_{35}N_3O_7$	72.79 / 72.71	5.15 / 5.09	6.12 / 6.06	167-169	93
3a	$C_{27}H_{18}N_2O_4$	74.58 / 74.65	4.23 / 4.18	6.40 / 6.45	187-189	71
3b	$C_{29}H_{22}N_2O_4$	75.33 / 75.31	4.86 / 4.79	6.14 / 6.06	193-195	67
3c	$C_{31}H_{26}N_2O_4$	75.97 / 75.90	5.33 / 5.34	5.76 / 5.71	152-154	88



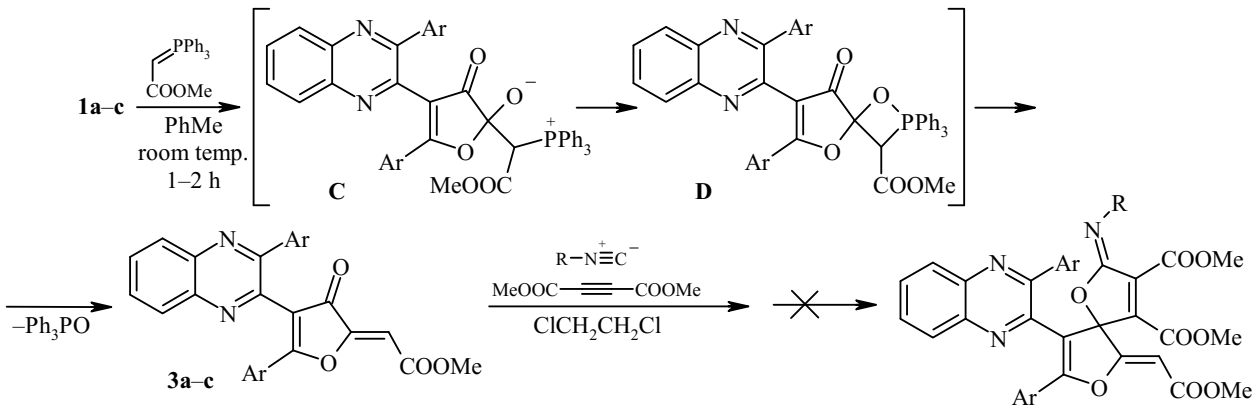
1a, **2a**,**d** Ar = Ph, **1b**, **2b**,**e** Ar = 4-MeC_6H_4, **1c**, **2c**,**f** Ar = 4-EtC_6H_4;
2a–**c** R = 1-adamantyl, **2d**–**f** R = 2-MeC_6H_4

The spectral characteristics of compounds **2a-f** matched those of the model compounds with structures confirmed by X-ray structural analysis [14] (Table 2).

Compounds **2a-f** apparently were formed through the zwitterionic intermediate **A**, which attacked the lactone carbonyl of the furan-2,3-diones **1a-c** leading to the intermediate compound **B**, which further cyclized to the respective spiro compounds **2a-f**.

In order to evaluate the possibility of an alternate pathway for this reaction (addition to the ketone carbonyl of the furan ring) we performed a reaction of the 5-aryl-4-(quinoxalin-2-yl)furan-2,3-diones **1a-c** with (methoxycarbonylmethylene)triphenylphosphorane and obtained new examples of substituted furan-3-ones: the 5-aryl-4-(quinoxalin-2-yl)furan-3-ones **3a-c**.

Compounds **3a-c** are yellow crystals with high melting points, readily soluble in chloroform, poorly soluble in acetonitrile, insoluble in water and hexane (Table 1).



3 a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-EtC_6H_4

TABLE 2. Spectral Characteristics of the Synthesized Compounds **2a-f** and **3a-c**

Compound	IR spectra, ν, cm^{-1}	^1H NMR spectra, δ, ppm (*J*, Hz)
2a	1762 (CO_2Me), 1740 (CO_2Me), 1723 (C=O), 1691 (C=N)	1.66-2.06 (15H, m, H Ad); 3.78 (3H, s, $COOCH_3$); 3.89 (3H, s, $COOCH_3$); 7.33-7.99 (12H, m, H Ar, H Ph); 8.16 (1H, d, *J* = 8.1, H Ar); 8.21 (1H, d, *J* = 7.8, H Ar)
2b	1752 (CO_2Me), 1736 (CO_2Me), 1720 (C=O), 1704 (C=N)	2.29 (3H, s, $ArC\underline{H}_3$); 2.32 (3H, s, $ArC\underline{H}_3$); 1.67-2.07 (15H, m, H Ad); 3.78 (3H, s, $COOCH_3$); 3.89 (3H, s, $COOCH_3$); 7.16 (2H, d, *J* = 8.1, H Ar); 7.23 (2H, d, *J* = 8.1, H Ar); 7.38 (2H, d, *J* = 7.8, H Ar); 7.46 (2H, d, *J* = 7.8, H Ar); 7.89-7.98 (2H, m, H Ar); 8.17 (1H, d, *J* = 8.1, H Ar); 8.19 (1H, d, *J* = 7.8, H Ar)
2c	1760 (CO_2Me), 1735 (CO_2Me), 1721 (C=O), 1705 (C=N)	1.10-1.18 (6H, m, $2CH_2C\underline{H}_3$); 1.68-2.07 (15H, m, H Ad); 2.53-2.64 (4H, m, $2C\underline{H}_2CH_3$); 3.79 (3H, s, $COOCH_3$); 3.89 (3H, s, $COOCH_3$); 7.15 (2H, d, *J* = 8.1, H Ar); 7.23 (2H, d, *J* = 8.1, H Ar) 7.32 (2H, d, *J* = 7.8, H Ar); 7.43 (2H, d, *J* = 7.8, H Ar); 7.88-7.98 (2H, m, H Ar); 8.16 (1H, d, *J* = 8.1, H Ar); 8.19 (1H, d, *J* = 7.8, H Ar)
2d	1752 (CO_2Me), 1736 (CO_2Me), 1723 (C=O), 1687 (C=N)	2.13 (3H, s, $ArC\underline{H}_3$); 3.85 (3H, s, $COOCH_3$); 3.99 (3H, s, $COOCH_3$); 7.05-8.22 (18H, m, H Ar, H Ph)
2e	1751 (CO_2Me), 1736 (CO_2Me), 1721 (C=O), 1692 (C=N)	2.15 (3H, s, $ArC\underline{H}_3$); 2.31 (3H, s, $ArC\underline{H}_3$); 2.51 (3H, s, $ArC\underline{H}_3$); 3.83 (3H, s, $COOCH_3$); 3.99 (3H, s, $COOCH_3$); 6.94-7.59 (14H, m, H Ar); 7.95 (1H, d, *J* = 8.1, H Ar); 8.19 (1H, d, *J* = 7.8, H Ar)
2f	1756 (CO_2Me), 1737 (CO_2Me), 1726 (C=O), 1690 (C=N)	1.10-1.15 (6H, m, $2CH_2C\underline{H}_3$); 2.16 (3H, s, $ArC\underline{H}_3$); 2.56-2.72 (4H, m, $2C\underline{H}_2CH_3$); 3.84 (3H, s, $COOCH_3$); 3.99 (3H, s, $COOCH_3$); 6.92-7.57 (14H, m, H Ar); 7.94 (1H, d, *J* = 8.1, H Ar); 8.18 (1H, d, *J* = 7.8, H Ar)
3a	1728 (CO_2Me), 1703 (C=O)	3.80 (3H, s, $COOCH_3$); 6.09 (1H, s, $=C\underline{H}COOMe$); 7.36-7.98 (12H, m, H Ar, H Ph); 8.15 (1H, d, *J* = 8.1, H Ar); 8.23 (1H, d, *J* = 7.8, H Ar)
3b	1725 (CO_2Me), 1709 (C=O)	2.33 (3H, s, $ArC\underline{H}_3$); 2.38 (3H, s, $ArC\underline{H}_3$); 3.88 (3H, s, $COOCH_3$); 6.09 (1H, s, $=C\underline{H}COOMe$); 7.10 (2H, d, *J* = 8.1, H Ar); 7.36 (2H, d, *J* = 8.1, H Ar); 7.43 (2H, d, *J* = 7.8, H Ar); 7.51 (2H, d, *J* = 7.8, H Ar); 8.12-8.15 (2H, m, H Ar); 8.21 (1H, d, *J* = 8.1, H Ar); 8.22 (1H, d, *J* = 7.8, H Ar)
3c	1723 (CO_2Me), 1701 (C=O)	1.12-1.18 (6H, m, $2CH_2C\underline{H}_3$); 2.54-2.67 (4H, m, $2C\underline{H}_2CH_3$); 3.80 (3H, s, $COOCH_3$); 6.06 (1H, s, $=C\underline{H}COOMe$); 7.18 (2H, d, *J* = 8.1, H Ar); 7.32 (2H, d, *J* = 8.1, H Ar) 7.39 (2H, d, *J* = 7.8, H Ar); 7.49 (2H, d, *J* = 7.8, H Ar); 7.89-7.99 (2H, m, H Ar); 8.14 (1H, d, *J* = 8.1, H Ar); 8.20 (1H, d, *J* = 7.8, H Ar)

The reaction was apparently initiated by a nucleophilic attack of (methoxycarbonylmethylene)-triphenylphosphorane at the lactone carbonyl of the furandione ring, leading to the formation of an intermediate betaine **C**, which further rearranged to the oxoazophosphetidine **D**, which transformed to compounds **3a**-**c** by elimination of triphenylphosphine oxide. A Wittig reaction of (methoxycarbonylmethylene)-triphenylphosphorane with substituted furan-2,3-diones was described previously, giving the product resulting from an addition at the lactone carbonyl group [15].

The attempts at three-component reactions of compounds **3a**-**c** with dimethyl acetylenedicarboxylate and isocyanide were not successful: separation of the reaction mixtures gave only the starting furan-3-ones **3a**-**c**. The reason for such a behavior of compounds **3a**-**c** was apparently in the sterically hindered approach to the ketone carbonyl of the furan ring, and the low reactivity of ester carbonyl groups.

Thus, we have established that the interaction of 5-aryl-4-(quinoxalin-2-yl)furan-2,3-diones, dimethyl acetylenedicarboxylate, and isocyanides gives single products from a reaction at the lactone carbonyl of the furan-2,3-diones, namely, dimethyl 7-aryl-8-(3-arylquinoxalin-2-yl)-2-(R-imino)-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylates.

EXPERIMENTAL

IR spectra were recorded on an FSM 1202 spectrometer in Nujol. The ^{1}H NMR spectra were acquired on a Mercury Plus 300 instrument (300 MHz) in DMSO-d_6, the internal standard was HMDS (δ 0.05 ppm). ^{13}C NMR spectra were acquired on a Mercury Plus 300 instrument (75 MHz) in $CDCl_3$ (compounds **2a**,**b**), and on a Bruker 500 instrument (125 MHz) in DMSO-d_6 (compounds **2d**,**e**), the internal standard was TMS. Mass spectra were recorded on a Kratos MS-30 instrument at 200°C temperature, with EI ionization (70 eV). Elemental analysis was performed on a Leco CHNS-932 analyzer. Melting points were determined on a PTP-2 apparatus. The individuality of the obtained compounds was confirmed by TLC on Sorbfil-TLC-A-UV plates, the eluents were EtOAc or hexane–EtOAc (5:3 and 5:1), the visualization was with iodine vapor. Dimethyl acetylenedicarboxylate was purchased from Sigma-Aldrich. Isocyanides used in this work were synthesized by known methods [16, 17].

Preparation of Compounds 2a-f (General Method). A solution of 5-aryl-4-(quinoxalin-2-yl)furan-2,3-dione **1a**-**c** (1.0 mmol) and dimethyl acetylenedicarboxylate (1.1 mmol) in anhydrous 1,2-dichloroethane (10 ml) was cooled to -10°C and added dropwise to a cold (-10°C) solution of the corresponding isocyanide (1.1 mmol) in anhydrous 1,2-dichloroethane (10 ml). The mixture was stirred at room temperature for 1-4 h. The solvent was removed, and the residue was crystallized by trituration with EtOH. The synthesized compounds were recrystallized from EtOH.

Dimethyl 2-(1-adamantylimino)-9-oxo-7-phenyl-8-(3-phenylquinoxalin-2-yl)-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylate (2a) was synthesized from 1-adamantylisocyanide and furan-2,3-dione **1a**. Colorless crystals. ^{13}C NMR spectrum, δ, ppm: 29.5, 36.3, 42.1 (C adamantane); 53.0 (OCH_3); 53.1 (OCH_3); 57.0 (C adamantane); 104.2 (C spiro); 114.0; 126.1; 128.1; 128.5; 128.7; 129.3; 129.8; 129.9; 130.0; 130.5; 130.6; 130.7; 131.4; 133.3; 134.6; 138.2; 138.6; 139.6; 141.5; 141.9; 144.5; 145.4; 147.8; 150.5; 154.7 (C=N); 159.4, 161.3, 190.0 (3C=O).

Dimethyl 2-(1-adamantylimino)-7-(4-methylphenyl)-8-[3-(4-methylphenyl)quinoxalin-2-yl]-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylate (2b) was synthesized from 1-adamantylisocyanide and furan-2,3-dione **1b**. Colorless crystals. ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 21.7 (CH_3); 29.5, 36.3, 42.1 (C adamantane); 53.0 (OCH_3); 53.1 (OCH_3); 56.9 (C adamantane); 104.1 (C spiro); 113.7; 125.3; 128.1; 128.6; 128.7; 129.1; 129.2; 129.3; 129.7; 130.5; 130.6; 131.2; 133.2; 134.4; 138.3; 138.8; 139.6; 141.6; 141.9; 144.5; 145.6; 147.8; 148.0; 150.5; 154.8 (C=N); 159.6, 161.3, 190.1 (3C=O).

Dimethyl 2-(1-adamantylimino)-7-(4-ethylphenyl)-8-[3-(4-ethylphenyl)quinoxalin-2-yl]-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylate (2c) was synthesized from 1-adamantylisocyanide and furan-2,3-dione **1c**. Colorless crystals.

Dimethyl 2-[(2-methylphenyl)imino]-9-oxo-7-phenyl-8-(3-phenylquinoxalin-2-yl)-1,6-dioxaspiro-[4.4]nona-3,7-diene-3,4-dicarboxylate (2d) was synthesized from *o*-methylphenylisocyanide and furan-2,3-dione **1a**. Yellow crystals. ^{13}C NMR spectrum, δ, ppm: 17.4 (CH_3); 53.8 (OCH_3); 54.0 (OCH_3); 104.8 (C spiro); 113.4; 121.2; 124.1; 126.1; 126.2; 126.3; 126.4; 126.7; 128.0; 128.2; 128.3; 128.4; 128.8; 128.9; 129.0; 129.1; 129.2; 130.5; 130.8; 131.5; 134.3; 136.2; 137.3; 139.6; 140.7; 141.1; 141.9; 143.5; 145.4; 150.5; 154.0 (C=N); 158.6, 160.1, 190.9 (3C=O). Mass spectrum, *m*/*z* ($I_{rel,}$ %): 637 $[M]^+$ (100).

Dimethyl 7-(4-methylphenyl)-2-[(2-methylphenyl)imino]-8-[3-(4-methylphenyl)quinoxalin-2-yl]-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylate (2e) was synthesized from *o*-methylphenylisocyanide and furan-2,3-dione **1b**. Colorless crystals. ^{13}C NMR spectrum, δ, ppm: 17.3 (CH_3); 20.8 (CH_3); 21.2 (CH_3); 53.8 (OCH_3); 53.9 (OCH_3); 104.8 (C spiro); 113.0; 121.3; 124.0; 126.1; 126.4; 126.9; 128.3; 128.4; 128.6; 128.8; 128.9; 129.0; 129.1; 129.8; 129.9; 130.5; 130.6; 131.4; 134.6; 136.2; 137.4; 138.6; 139.6; 140.6; 141.1; 141.8; 143.5; 145.3; 145.5; 150.5; 153.9 (C=N); 158.6, 160.1, 190.0 (3C=O).

Dimethyl 7-(4-ethylphenyl)-8-[3-(4-ethylphenyl)quinoxalin-2-yl]-2-[(2-methylphenyl)imino]-9-oxo-1,6-dioxaspiro[4.4]nona-3,7-diene-3,4-dicarboxylate (2f) was synthesized from *o*-methylphenylisocyanide and furan-2,3-dione **1c**. Yellow crystals.

Preparation of Compounds 3a-c (General Method). A solution of the corresponding 5-aryl-4-(quinoxalin-2-yl)furan-2,3-dione **1a-c** (1 mmol) in anhydrous toluene (5 ml) was stirred for 10 min, then a solution of (methoxycarbonylmethylene)triphenylphosphorane (1 mmol) in anhydrous toluene (5 ml) was added dropwise. The mixture was stirred at room temperature for 1-2 h. The solvent was evaporated (except in the case of compound **3b**, which precipitated without removal of the solvent); the residue was crystallized by trituration with MeCN. The synthesized compounds were recrystallized from MeCN.

Methyl 2-[3-oxo-5-phenyl-4-(3-phenylquinoxalin-2-yl)-2(3*H*)-furanylidene]acetate (3a) was synthesized from furan-2,3-dione **1a**. Yellow crystals. Mass spectrum, *m*/*z* ($I_{rel,}$ %): 434 $[M]^+$ (84).

Methyl 2-{5-(4-methylphenyl)-4-[3-(4-methylphenyl)quinoxalin-2-yl]-3-oxo-2(3*H*)-furanylidene}-acetate (3b) was synthesized from furan-2,3-dione **1b**. Yellow crystals. Mass spectrum, *m*/*z* ($I_{rel,}$ %): 462 $[M]^+$ (100).

Methyl 2-{5-(4-ethylphenyl)-4-[3-(4-ethylphenyl)quinoxalin-2-yl-3-oxo]-2(3*H*)-furanylidene}acetate (3c) was synthesized from furan-2,3-dione **1c**. Yellow crystals. Mass spectrum, *m*/*z* ($I_{rel,}$ %): 490 $[M]^+$ (21).

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