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SYNTHESIS AND PROPERTIES OF Z-1,3-BIS-(ARYL)-4-BROMO-2-BUTEN-1-ONES

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Bromination of 1,3-bis(aryl)-2-buten-1-ones by N-bromosuccinimide in anhydrous carbon tetrachloride gives Z-1,3-bis(aryl)-4-bromo-2-buten-1-ones. The effect of the nature of substituent in the benzene ring on the course of a reaction with nucleophiles has been studied. Heating an alcohol solution of these ketones (Ar = 4-$MeOC_6H_4$, 4-ClC_6H_4) in the presence of acid or in the presence of base (Ar = Ph) gave 2,4-bis(aryl)furans. Treatment of 1,3-bis(aryl)-4-bromo-2-buten-1-ones with thioacetamide gave 2,4-bis(aryl)thiophenes. The oxidation of the halo-substituted dypnones with H_2O_2/NaOH gave (3-bromomethyl-3-aryl-2-oxiranyl)(aryl)methanones. The reaction of halo-substituted dypnones with aryl hydrazines gave 1,3,5-triaryl-1,6-dihydropyridazines or 1,3,5-triarylpyridazinium bromides depending on the structure of the reagents.

Keywords: 2,4-bis(aryl)thiophene, 2,4-bis(aryl)furan, γ-bromodypnone, α-bromodiphenacyl, 1,3,5-triaryl-1,6-dihydropyridazine.

γ-Halocarbonyl compounds are convenient building blocks for the synthesis of different carbo- and heterocyclic compounds [1]. Amongst these, γ-halo-substituted unsaturated ketones (α-halo ketone vinylogs) are difficult to obtain and so have been little studied. In a number of cases the vinylogous homologation [2, 3] of α-halo ketones can lead to an unexpected reaction course and to the appearance of products totally uncharacteristic of the starting compounds. Data in the literature for the reactions of γ-halo-substituted unsaturated ketones points to the existence of a marked structural effect on the course of their reaction with different nucleophiles [4, 5]. The aim of this work was to determine the effect of the nature of the substituent in the benzene ring of the 1,3-bis(aryl)-4-bromo-2-buten-1-ones **1a-d** on their reactivity towards several nucleophiles (previously studied in the case of the 4-bromo-1,3-diphenyl-2-buten-1-one (γ-bromodypnone, **1b**, [5-8])). According to our data problems of this type are not covered in the literature.

The preparation of the 1,3-bis(aryl)-4-bromo-2-buten-1-ones **1a,c,d** used the procedure developed before for the synthesis of the γ-bromodypnone **1b** [8]. Bromination of the 1,3-bis(aryl)-4-bromo-2-buten-1-ones **2a,c,d** using N-bromosuccinimide in anhydrous carbon tetrachloride gave the target products **1a,c,d** in good yields (55-75%). The presence of a substituent in the benzene ring did not have a marked effect on the method of preparing compound **1** but an increase in the electron acceptor properties of the substituent showed a tendency towards the decreasing formation of side reaction products.

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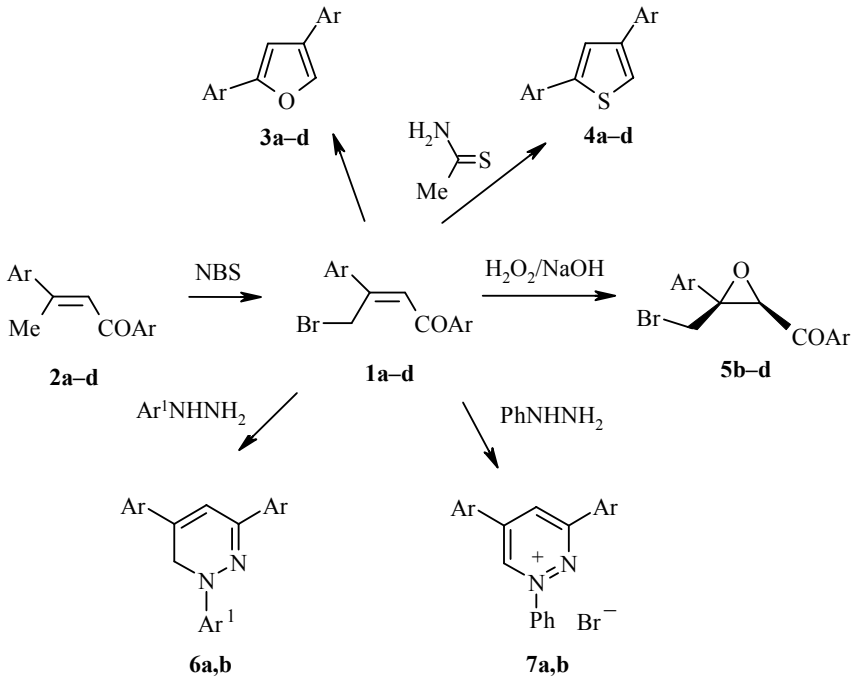

1–5 a Ar = 4-$MeOC_6H_4$, **b** Ar =Ph, **c** Ar = 4-ClC_6H_4, **d** Ar = 4-BrC_6H_4;
6 a Ar = 4-ClC_6H_4, Ar^1 = 4-$O_2NC_6H_4$, **b** Ar = 4-BrC_6H_4, Ar^1 =Ph;
7 a Ar = 4-ClC_6H_4, **b** Ar = 4-BrC_6H_4

The structure of γ-bromodypnone **1b** as the *Z*-isomer was reliably established previously [8, 9] through its chemical and spectroscopic properties. It is apparent that, using the same conditions, the *Z*-isomers would also be expected in the case of the substituted ketones **2**. In order to verify this proposal the UV spectra of the novel compounds **1a,c,d** were recorded. Their methanol solutions showed a characteristic maximum absorption for the *Z*-γ-bromodypnone **1b** [9] at 286-302 nm with ε 19,500-24,000. As in the case of **1b**, short irradiation (5-7 min, mercury lamp) of the solutions of compounds **1a,c,d** gave a hypsochromic shift for the long wavelength band of 30-50 nm caused by conversion of *Z*- to *E*-isomers [9]. Attempts to separate the latter proved unsuccessful, evaporation of solvent giving the *Z*-structured starting compounds.

The *cis* orientation of the functional groups in the 1,3-bis(aryl)-4-bromo-2-buten-1-ones **1** results in ready formation of cyclic products. Intramolecular cyclization of compounds **1a-d** gives the 2,4-bis(aryl)furans **3a-d** and can take place upon heating solutions of compound **1** in neutral (ethanol), acid (ethanol + HCl), or base (ethanol + Na_2CO_3) medium. The substituent in the benzene ring of starting compound **1** proved to have a marked effect on the rate of formation of the product **3**. Hence, when carrying out the reaction without catalyst the conversion of compounds **1a** to **3a** occurs over 30-40 min. The preparation of furan **3b** needs longer heating (3 h) [10] but the halo-substituted dypnones **1c,d** proved stable under these conditions. In the presence of acid or base the conversion of compounds **1** to furans **3** occurs more rapidly with preservation of the overall tendency of decreasing reactivity from **1a** to **1d**. In addition, in the case of compounds **1a,b** the reaction is accompanied by the formation of a large amount of side products. The furan **3c** was obtained in satisfactory yield by heating an alcohol solution of compound **1c** in the presence of acid. With the use of the *p*-bromo-substituted γ-bromodypnone **1d** the furan **3d** is formed only with prolonged heating in the presence of base (Na_2CO_3).

We have previously found [6] that heating the γ-bromodypnone **1b** with thioacetamide in ethanol gives the 2,4-diphenylthiophene (**4b**). The 2,4-bis(aryl)thiophenes **4a,c,d** were obtained from compounds **1a,c,d**

under the same conditions. In this case the rate of formation of the reaction products **4** follows the same dependence with an increase in the electronegativity of the substituent in the benzene ring correlating with an increase in the time for heating the reaction mixture from 10 min for **1a** to 2 h for **1d**.

α,β-Unsaturated ketones readily form epoxy derivatives *via* direct oxidation with hydrogen peroxide in the presence of base [11]. In the case of the γ-bromodypnone **1b** this reaction had been studied in detail previously [8, 9]. We have shown that the halo-substituted dypnones **1c,d** can also be converted to the corresponding (3-aryl-3-bromomethyl-2-oxiranyl)(aryl)methanones **5c,d** in the conditions indicated. However, in contrast to the γ-bromodypnone **1b**, the preparation of oxiranes **5c,d** needs heating of the reaction mixtures. Compound **1a** gives a complex mixture of products upon treatment with strong bases, even with cooling. A comparison of the melting points of the oxiranes **5c,d** prepared with literature data [12, 13] points to the formation of *trans* isomers.

We have previously shown [14] that the formation of arylhydrazones as a characteristic of ketones occurs with greater complexity for the γ-bromodypnone **1b** and can lead to acylhydrazone or cyclic products depending on the conditions and the structure of the hydrazine. The reaction of γ-bromo ketones **1c,d** with arylhydrazines gives exclusively cyclic 1,3,5-triarylpyridazine products. Independently of the structure of the arylhydrazine and the reaction conditions, compound **1a** gives furan **3a**.

A factor determining the result of the reaction is the nature of the substituent in both reagents. As in the example of the γ-bromodypnone **1b** [14], heating compound **1c** with 4-nitrophenylhydrazine in alcohol gives a 1,6-dihydropyridazine derivative which is 3,5-bis(4-chlorophenyl)-1-(4-nitrophenyl)-1,6-dihydropyridazine (**6a**). The more inert *p*-bromo-substituted γ-bromodypnone **1d** reacts very slowly with 4-nitrophenylhydrazine hence prolonged (24 h) heating gives a complex mixture containing mainly the starting ketone.

By contrast with compound **1b,** compounds **1c,d** react with phenylhydrazine exclusively upon heating. Compound **1c** gives the 1-phenyl-3,5-bis(4-chlorophenyl)pyridazin-1-ium bromide (**7a**) and compound **1d** gives the 3,5-bis(4-bromophenyl)-1-phenyl-1,6-dihydropyridazine (**6b**). In the latter case a solid product was also obtained from the reaction mixture and this proved to be a mixture which contained 40% of the 3,5-bis-(4-bromophenyl)-1-phenylpyridazin-1-ium salt (**7b**). It should be noted that the it is possible to stop reaction of the γ-bromo ketone **1b** with phenylhydrazine at an earlier reaction stage to give the 1,3,5-triphenyl-1,6- and 1,3,5-triphenyl-1,4-dihydropyridazine arylhydrazone [14]. An increase in the length of heating the reaction mixture or the presence of a strong acid leads to aromatization of the product.

The observed results of the reaction of bromo ketones **1c,d** with arylhydrazines can be explained in the following way. Introduction of electron acceptor substituents into the 1,6-dihydropyridazine system lowers its basicity and increases the stability towards oxidation [14, 15]. On the other hand, the lowered reactivity of the γ-bromo ketones **1c,d** leads to an increase in the reaction mixture heating time and this offers the right conditions for further oxidation to the pyridazinium salt **7**. In the case of the γ-bromo ketone **1d** the low solubility of the reaction product **6b** in alcohol removes the major part of it from the reaction mixture and avoids its subsequent oxidation.

The conclusions regarding the structure of the reaction products **6, 7** were made on the basis of their ^{1}H NMR spectroscopic data. In this case, the criteria for assigning the structure are the presence and position of a signal for the methylene group protons. The spectra of compounds **6a,b** show a two proton singlet at 4.85 (**6a**) and 4.70 ppm (**6b**) in the region characteristic of 1,6-dihydropyridazines [14]. The absence of signals in the aliphatic part of the spectrum of product **7a** and the presence of one proton singlets at 10.64 (H-6) and 9.53 ppm (H-4) point to the formation of the aromatic 1,3,5-trisubstituted pyridazinium system.

Hence we can conclude that the reactivity of the 1,3-bis(aryl)-4-bromo-2-buten-1-one system depends on the nature of the substituent in the benzene ring. For reactions carried out in a protonic solvent (alcohol) lowering of the donor properties of the substituent leads to a decrease in reactivity which correlates with the Hammett σ constant for the *para* substituent [16]. The result of introducing electron acceptor substituents into the 1,3-bis(aryl)-4-bromo-2-buten-1-one structure is an increase in their stability and decreased tendency to

form products of intramolecular cyclization upon heating in the presence of base. The introduction of donor substituents leads to a reversed effect which lowers the likelihood of forming the target products in reactions with nucleophiles.

In order to assess the biological potential of the 1,3-bis(aryl)-4-bromo-2-buten-1-ones reported in this work a spectrum of their biological activity was calculated. The PASS (Prediction of Activity Spectra for Substances) [17-19] program was used in these calculations. Basically the selection of active compounds involves a multilevel assessment of the closest environment of the atoms and comparison of the calculated 2D descriptors with a set of those corresponding to likely appearance of either high compound activity or of inactivity. The final result of the program is a schedule of the likely appearance of compound activity (p_a) or inactivity (p_i) in fractional units. A spectrum of more than 3000 types of activity was calculated for each compound with the activity threshold set at $p_a > 0.9$ and $p_i < 0.02$. Amongst the activity characterizing compounds **1a-d** there is observed the prediction of an efficient inhibition of the synthesis of protein structures in terms of non specific inhibition of the enzyme systems: prolyl aminopeptidases, phosphoenolpyruvate protein phosphotransferases, (-)-(4S)-limonene synthases, and threonine aldolases.

EXPERIMENTAL

IR spectra were recorded on a Pye-Unicam SP3-300 instrument for CsI tablets. ^{1}H NMR spectra were taken on a Varian Mercury 400 (400 MHz) instrument using DMSO-d_6 with TMS as internal standard. UV spectra were obtained in methanol on a Lambda 20 UV/VIS spectrometer. Irradiation of compounds **1a-d** was carried out using a PRK-4 mercury lamp. Monitoring of the reaction course and the purity of the compounds obtained was carried out using TLC on Silufol UV-254 plates.

1,3-Bis(aryl)-2-buten-1-ones 2a,c,d were prepared by method [20].

Compound 2a. Yield 60%; mp 94-96ºC (EtOH), mp 95ºC [21].

Compound 2c. Yield 75%; mp 74-76ºC (EtOH), mp 79ºC [22].

Compound 2d. Yield 70%; mp 105-106ºC (EtOH), mp 107ºC [23].

Z-1,3-Bis(aryl)-4-bromo-2-buten-1-ones 1a,c,d. N-Bromosuccinimide (8.9 g, 50 mmol) was added to a solution of the 1,3-bis(aryl)-2-buten-1-ones **2a,c,d** (50 mmol) in anhydrous carbon tetrachloride (50 ml). The mixture was heated to reflux, benzoyl peroxide (0.3 g) was added, and the product was refluxed for 1-1.5 h. It was cooled and succinimide filtered off. The solvent was evaporated and the residue was recrystallized from 2-propanol.

Compound 1a. Yield 9.93 g (55%); mp 92-93ºC (from 2-propanol). IR spectrum, ν, cm^{-1}: 1640 (C=O), 1600, 1570, 1485, 1297, 1265, 1220, 1178 (C–O); 1030 (C–O); 828. UV spectrum (MeOH), λ_{max}, nm ($\varepsilon\times10^{-3}$): 226 (22.28), 286 (19.55). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.06 (2H, d, ^3J = 8.5, H-2',6'); 7.77 (2H, d, ^3J = 8.5, H-2",6"); 7.41 (1H, s, H-2); 7.05 (2H, d, ^3J = 8.5, H-3',5'); 7.02 (2H, d, ^3J = 8.5, H-3",5"); 5.07 (2H, s, H-4); 3.85 (3H, s, 4'-OCH_3); 3.82 (3H, s, 4"-OCH_3). Found, %: C 59.80; H 4.65; Br 22.15. $C_{18}H_{17}BrO_3$. Calculated, %: C 59.85; H 4.74; Br 22.12.

Compound 1c. Yield 13.88 g (75%); mp 107-108ºC (2-propanol). IR spectrum, ν, cm^{-1}: 1698 (C=O), 1595, 1490, 1410, 1215, 820. UV spectrum (MeOH), λ_{max}, nm ($\varepsilon\times10^{-3}$): 226 (23.48), 298 (22.69). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.09 (2H, d, ^3J = 8.0, H-2',6'); 7.84 (2H, d, ^3J = 8.0, H-2",6"); 7.61 (2H, d, ^3J = 8.0, H-3',5'); 7.55 (2H, d, ^3J = 8.0, H-3",5"); 7.48 (1H, s, H-2); 5.02 (2H, s, H-4). Found, %: C 51.84; H 2.92; Br 21.61; Cl 19.19. $C_{16}H_{11}BrCl_2O$. Calculated, %: C 51.93; H 3.00; Br 21.59; Cl 19.16.

Compound 1d. Yield 16.06 g (70%); mp 117-119ºC (2-propanol). IR spectrum, ν, cm^{-1}: 1705 (C=O), 1585, 1210, 1070, 1055, 1010, 995, 825. UV spectrum (MeOH), λ_{max}, nm ($\varepsilon\times10^{-3}$): 230 (25.32), 274 (25.10), 302 (24.00). ^{1}H NMR Spectrum, δ, ppm (*J*, Hz): 7.99 (2H, d, ^3J = 8.0, H-2',6'); 7.71 (2H, d, ^3J = 8.0, H-2",6"); 7.68 (2H, d, ^3J = 8.0, H-3',5'); 7.60 (2H, d, ^3J = 8.0, H-3",5"); 7.40 (1H, s, H-2); 5.01 (2H, s, H-4). Found, %: C 41.79; H 2.33; Br 52.24. $C_{16}H_{11}Br_3O$. Calculated, %: C 41.87; H 2.42; Br 52.23.

2,4-Bis(4-methoxyphenyl)furan (3a). A solution of compound **1a** (0.4 g, 1.1 mmol) in ethanol (10 ml) was refluxed for 40 min. After cooling the precipitate was filtered off, washed with ethanol and crystallized from ethanol. Yield 0.25 g (80%); mp 190-192ºC, mp 192ºC [24].

2,4-Bis(4-chlorophenyl)furan (3c). Conc. HCl (1 ml) was added to a solution of compound **1c** (0.4 g, 1.08 mmol) in ethanol (10 ml) and refluxed for 1 h. After cooling the precipitate was filtered off, washed with ethanol, and crystallized from ethanol. Yield 0.17 g (56%); mp 127-129ºC, mp 128ºC [24].

2,4-Bis(4-bromophenyl)furan (3d). Na_2CO_3 (0.1 g, 1.0 mmol) was added to a solution of compound **1d** (0.4 g, 0.87 mmol) in ethanol (20 ml) and refluxed for 3 h. After cooling, the precipitate was filtered off, thoroughly washed with water and ethanol, and recrystallized from nitromethane to give the product (0.13 g, 40%) with mp 159-160ºC and mp 160ºC [24].

2,4-Bis(aryl)thiophenes 4a,c,d. Thioacetamide (0.15 g, 2.0 mmol) was added to a solution of compound **1a,c,d** (2.0 mmol) in ethanol (30 ml) and the mixture obtained was refluxed for 10 min (in the case of compound **1a**), 50 min (compound **1c**), or 2 h (compound **1d**). The product was cooled and the precipitate was filtered and washed with alcohol.

Compound 4a. Yield 0.30 g (51%); mp 219-220ºC (EtOH), mp 221ºC [25].

Compound 4c. Yield 0.38 g (62%); mp 139-140ºC ($MeNO_2$), mp 140ºC [26].

Compound 4d. Yield 0.44 g (56%); mp 173-175ºC ($MeNO_2$), mp 174.5ºC [26].

[(2*R*,3*S*)-3-Aryl-3-bromomethyl-2-oxiranyl](aryl)methanones 5c,d. H_2O_2 (30%, 2 ml) and NaOH solution (1N, 1 ml) were added with stirring to a solution of compound **1c,d** (0.65 mmol) in ethanol (10 ml) and the mixture was stirred at 40-50ºC for 1 h. Water (30 ml) was added and the precipitate was filtered, thoroughly washed with water and alcohol, and recrystallized from 2-propanol.

Compound 5c. Yield 0.14 g (54%); mp 131-132ºC (2-propanol), mp 131ºC [12].

Compound 5d. Yield 0.20 g (65%); mp 119-120ºC (2-propanol), mp 119ºC [13].

3,5-Bis(4-chlorophenyl)-1-(4-nitrophenyl)-1,6-dihydropyridazine (6a). A mixture of compound **1c** (0.4 g, 1.08 mmol) and 4-nitrophenylhydrazine (0.2 g, 1.08 mmol) in ethanol (20 ml) was refluxed for 3 h, cooled, and the precipitate formed was filtered off and washed with alcohol. Yield 0.27 g (60%); mp 250-253ºC (decomp., $MeNO_2$). IR spectrum, ν, cm^{-1}: 1580, 1495, 1320, 1280, 1165, 1085, 810. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.20 (2H, d, ^3J = 9.0, H-3',5'); 8.01 (2H, d, ^3J = 8.0, H-2",6"); 7.96 (2H, d, ^3J = 8.0, H-2"',6"'); 7.66 (2H, d, ^3J = 9.0, H-2',6'); 7.48 (2H, d, ^3J = 8.0, H-3",5"); 7.44 (2H, d, ^3J = 8.0, H-3"',5"'); 7.33 (1H, s, H-4); 4.85 (2H, s, H-6). Found, %: C 62.21; H 3.49; Cl 16.75; N 9.91. $C_{22}H_{15}Cl_2N_3O_2$. Calculated, %: C 62.28; H 3.56; Cl 16.71; N 9.90.

3,5-Bis(4-bromophenyl)-1-phenyl-1,6-dihydropyridazine (6b). A mixture of compound **1d** (0.4 g, 0.87 mmol) and phenylhydrazine (0.01 ml, 1 mmol) in ethanol (20 ml) was refluxed for 1 h. The product was cooled and the precipitate was filtered off, washed with alcohol, and recrystallized from nitromethane to give 0.27 g (67%) with mp 143-145ºC (nitromethane). IR spectrum, ν, cm^{-1}: 1600, 1595, 1210, 1080, 1010, 805. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.88 (2H, d, ^3J = 8.0, H-2",6"); 7.79 (2H, d, ^3J = 8.0, H-2"',6"'); 7.62-7.47 (6H, m, H-2',6', H-3",5", H-3"',5"'); 7.34 (2H, t, ^3J = 8.0, H-3',5'); 7.24 (1H, s, H-4); 6.98 (1H, t, ^3J = 8.0, H-4'); 4.70 (2H, s, H-6). Found, %: C 56.37; H 3.39; Br 34.18; N 6.00. $C_{22}H_{16}Br_2N_2$. Calculated, %: C 56.44; H 3.44; N 5.98.

3,5-Bis(4-chlorophenyl)-1-phenylpyridazin-1-ium Bromide (7a). A mixture of compound **1c** (0.4 g, 1.08 mmol) and phenylhydrazine (0.11 ml, 1.08 mmol) in ethanol (20 ml) was refluxed for 2 h. Solvent was evaporated and the residue was treated with methyl *tert*-butyl ether (10 ml). The precipitate formed was filtered off and washed with ether to give 0.24 g (48%) with mp 321-323ºC (decomp., 2-propanol). IR spectrum, ν, cm^{-1}: 1595, 1390, 1090, 820, 752. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.64 (1H, s, H-6); 9.53 (1H, s, H-4); 8.50 (4H, m, H-2',6', H-2",6"); 8.29 (2H, m, H-2"',6"'); 7.79 (3H, m, H-3'-H-5'); 7.71 (4H, m, H-3",5", H-3"',5"'). Found, %: C 57.63; H 3.28; Br 17.45; Cl 15.46; N 6.14. $C_{22}H_{15}BrCl_2N_2$. Calculated, %: C 57.67; H 3.30; Br 17.44; Cl 15.48; N 6.11.

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