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# Synthesis of furan and dihydrofuran derivatives *via* Feist–Benary reaction in the presence of ammonium acetate in aqueous ethanol

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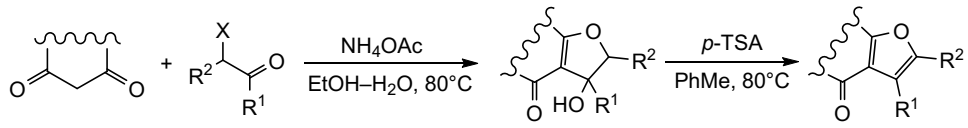



$R^1 = CO_2Et$, $R^2 = H$; $R^1 = Me$, $R^2 = CO_2Et$, COMe

An efficient synthesis of dihydrofurans and furans by a reaction between 1,3-dicarbonyl compounds and ethyl bromopyruvate, ethyl 2-chloroacetoacetate, or 3-chloroacetylacetone in the presence of ammonium acetate in aqueous ethanol is described. When the reaction was performed with a phenacyl bromide, *O*-alkylation of 1,3-dicarbonyl compounds occurred without cyclization.

**Keywords**: 1,3-dicarbonyl compounds, dihydrofuran, ethyl bromopyruvate, furan, phenacyl bromide, Feist–Benary reaction.

The Feist–Benary reaction involves condensation of 1,3-dicarbonyl compounds with α-halo ketones to produce substituted furans.[1,2] However, running the reaction under modified conditions allowed the isolation of a dihydrofuran intermediate. Several groups studied the mechanism and scope of this so-called "interrupted" Feist–Benary reaction.[3,4] Most publications concerning this reaction have been aimed at studying its catalytic asymmetric version with particular emphasis of the diastereoselectivity and enantioselectivity issues.[4b,c,5–8] Furans, as well as di- and tetrahydrofurans are constituents of many natural products arising from plants and marine organisms with promising biological activities.[9–12]

As a part of the recent trend of developing new methods of heterocyclic synthesis in water,[13–15] we wish to report an efficient synthesis of functionalized dihydrofurans and furans by the reaction of 1,3-dicarbonyl compounds **1a**–**d** with α-halo ketones in the presence of ammonium acetate in aqueous ethanolic solution. The reaction of 1,3-dicarbonyl compounds **1a**–**d** with ethyl bromopyruvate (**2**) thus led to dihydrofurans **3a**–**d** in good yields (Scheme 1). The isolation of products in this method is easier than in other described methods, and the reaction is more environment-friendly because of solvent used (aqueous ethanol); in addition, the yields of the products are higher. Compounds **3a**–**d** were converted to the corresponding furan derivatives **4a**–**d** in the presence of *p*-toluenesulfonic acid (*p*-TSA).

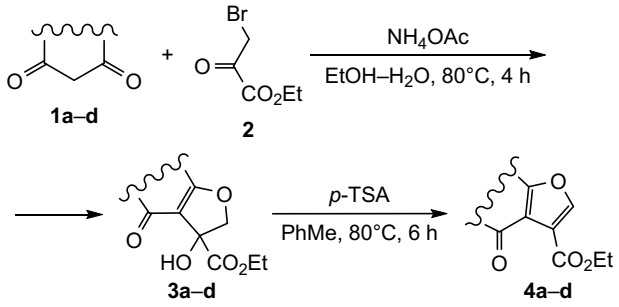
However, under similar conditions the reactions of α-halo ketones, 3-chloropentane-2,4-dione (**5a**) and methyl 2-chloro-3-oxobutanoate (**5b**), with 1,3-dicarbonyl compounds **1b**–**d** led directly to fused furan derivatives **6a**–**e** in good yields (Scheme 2). The structures of compounds **3a**–**d**, **4a**–**d**, **6a**–**e** were confirmed by IR, $^1$H and $^{13}$C NMR spectroscopy and mass spectrometry.

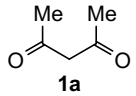
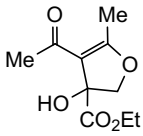
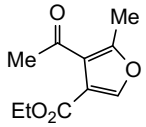
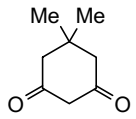
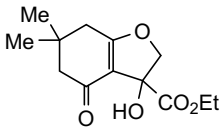
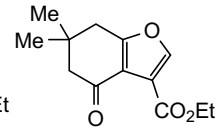
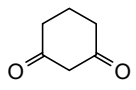
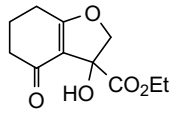
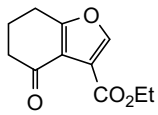
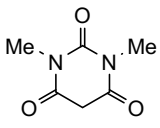
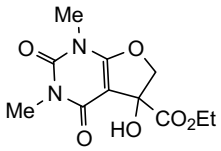
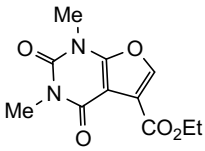
Under similar conditions the reaction of 4'-bromophenacyl bromides (**7**) with 1,3-dicarbonyl compounds **1b**,**c** led to esters **8a**,**b** (Scheme 3).

Structure of the isolated products **8a**,**b** was determined on the basis of their elemental analyses, as well as their IR, $^1$H and $^{13}$C NMR spectroscopy and mass spectrometry data. The $^1$H NMR spectrum of compound **8a** in $CDCl_3$ showed five sharp singlets arising from $C(CH_3)_2$ (1.10 ppm), $CH_2$ (2.23, 2.44, and 5.10 ppm), and methine (5.20 ppm) protons.

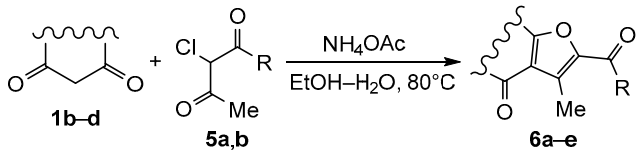
The proposed mechanism of this reaction is presented in Scheme 4. The reaction likely starts as a *C*-acylation of enolate **9** with the formation of a 1:1 adduct **10** between the 1,3-dicarbonyl compound **1** and α-halo ketones **2**, **5**. Adduct **10** undergoes intramolecular cyclization to produce dihydrofurans of type **3**, which are converted to furans by elimination of $H_2O$. In the case of phenacyl bromide **7**, its carbonyl group is involved in resonance with the aryl ring, thus the nucleophilic attack is directed towards α-carbon of compound **1**. Thus, steric factors might lead to a preferential *O*-alkylation of enolate **9** to give ethers **8**.

**Scheme 1**

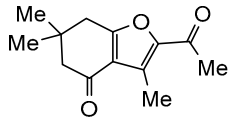
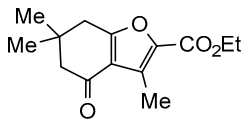
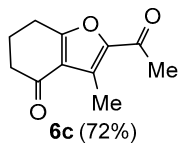
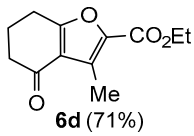
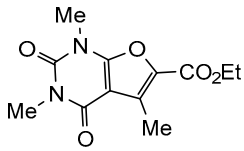



| 1,3-Dicarbonyl compound | Dihydrofuran | Furan |
|---|---|---|
|  **1a** |  **3a** (88%) |  **4a** (89%) |
|  **1b** |  **3b** (97%) |  **4b** (96%) |
|  **1c** |  **3c** (88%) |  **4c** (87%) |
|  **1d** |  **3d** (93%) |  **4d** (91%) |

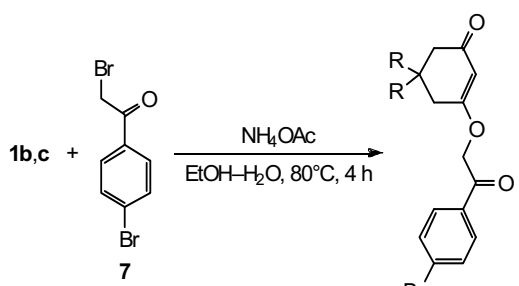
**Scheme 2**



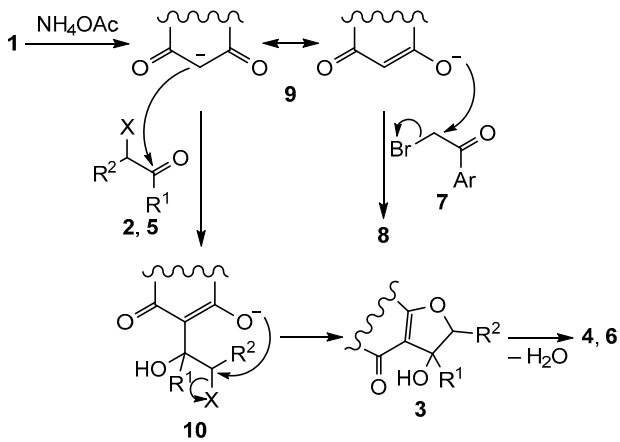

**5 a** R = Me, **b** R = OEt

| 1,3-Dicarbonyl compound | α-Chlorocarbonyl compound | Furan |
|---|---|---|
| **1b** | **5a** |  **6a** (83%) |
| **1b** | **5b** |  **6b** (76%) |
| **1c** | **5a** |  **6c** (72%) |
| **1c** | **5b** |  **6d** (71%) |
| **1d** | **5b** |  **6e** (69%) |

**Scheme 3**




**Scheme 4**



The reaction between 1,3-dicarbonyl compounds and α-halo ketones in the presence of ammonium acetate in aqueous ethanol leads, depending on the structure of the α-halo ketone, to highly substituted dihydrofurans or furans, or open-chain *O*-alkylation products. For the purpose of synthesizing furan derivatives, the simplicity of this procedure makes it an interesting alternative to complex multistep approaches in view the environment-friendly conditions and availability of the starting materials.

## Experimental

IR spectra were recorded on a Shimadzu IR-460 spectrometer in KBr. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DRX-300 instrument (300 and 75 MHz, respectively) in acetone-$d_6$ (compounds **6a**,**d**) or $CDCl_3$ (other compounds) with TMS as internal standard. Electron ionization mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. Melting points were determined on an Electrothermal 9100 apparatus. Preparative column chromatography was performed on silica gel (Merck 230–400 mesh). All chemicals were purchased from Fluka and used without further purification.

**Preparation of dihydrofuran-3-carboxylates 3a–d** (General method). A mixture of the 1,3-dicarbonyl compound **1** (2 mmol) and ammonium acetate (0.14 g, 2 mmol) in EtOH–$H_2O$, 7:3 (5 ml) was stirred at 80°C for about 1 h. Then ethyl bromopyruvate (**2**) (0.39 g, 2 mmol) was added to the reaction mixture, and the stirring was continued for 3 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography using *n*-hexane–AcOEt, 4:1, as eluent. Products **3a**–**c** have been reported previously.[4b]

**Ethyl 5-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydrofuro[2,3-*d*]pyrimidine-5-carboxylate (3d)**. Yield 0.5 g (93%), white powder, mp 166–168°C. IR spectrum, ν, cm$^{-1}$: 3438, 2924, 2359, 1644, 1463, 1388, 1114. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, $^3J$ = 6.9, $CH_2C\underline{H}_3$); 3.30 (3H, s, $CH_3$); 3.40 (3H, s, $CH_3$); 4.19 (1H, br. s, OH); 4.36–4.39 (2H, m, $CH_2O$); 4.84 (1H, d, $^2J$ = 9.9) and 5.12 (1H, d, $^2J$ = 9.9, $CH_2$). $^{13}$C NMR spectrum, δ, ppm: 14.4, 28.2, 29.8 ($3CH_3$); 63.7 ($OCH_2$); 80.2 ($CH_2$); 84.4, 91.7, 151.7 (3C); 159.3, 164.2, 171.9 (3C=O). Found, %: C 48.63; H 5.51; N 10.51. $C_{11}H_{14}N_2O_6$. Calculated, %: C 48.89; H 5.22; N 10.37.

**Preparation of furan-3-carboxylates 4a–d** (General method). *p*-Toluenesulfonic acid (0.34 g, 0.5 mmol) was added to a stirred solution of compound **3a**–**d** (2 mmol) in toluene (10 ml). The reaction mixture was stirred at 80°C for 6 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography using hexane–AcOEt, 6:1, as eluent. Products **4a**–**c** have been reported previously.[4b]

**Ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrofuro-[2,3-*d*]pyrimidine-5-carboxylate (4d)**. Yield 0.46 g (91%), white powder, mp 140–142°C. IR spectrum, ν, cm$^{-1}$: 3434, 2925, 1747, 1671, 1524, 1260, 1101, 1017. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.40 (3H, t, $^3J$ = 7.1, $CH_2C\underline{H}_3$); 3.43 (3H, s, $CH_3$); 3.58 (3H, s, $CH_3$); 4.39 (2H, q, $^3J$ = 7.1, $OCH_2$); 7.80 (1H, s, CH). $^{13}$C NMR spectrum, δ, ppm: 14.6, 29.0, 29.9 ($3CH_3$); 61.8 ($OCH_2$); 94.9, 119.0, 150.6 (3C); 143.7 (CH); 156.8, 156.9, 161.3 (3C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 252 [M]$^+$ (100), 195 (91), 167 (77), 123 (28), 95 (46), 66 (46). Found, %: C 52.32; H 4.71; N 11.21. $C_{11}H_{12}N_2O_5$. Calculated, %: C 52.38; H 4.80; N 11.11.

**Preparation of fused furans 6a–e** (General method). A mixture of the 1,3-dicarbonyl compound **1b**–**d** (2 mmol) and ammonium acetate (0.14 g, 2 mmol) in EtOH–$H_2O$, 7:3, (5 ml) was stirred at 80°C for 1 h. Then α-halo ketone **5a**,**b** (2 mmol) was added and the stirring was continued at 80°C for additional 3 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography using hexane–AcOEt, 4:1, as eluent.

**2-Acetyl-3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (6a)**. Yield 0.36 g (83%), white powder, mp 132–134°C. IR spectrum, ν, cm$^{-1}$: 2938, 1683, 1661, 1591, 1226, 1113, 676. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (6H, s, $2CH_3$); 2.40 (2H, s, $CH_2$); 2.51 (2H, s, $CH_2$); 2.85 (3H, s, $CH_3$); 2.89 (3H, s, $CH_3$). $^{13}$C NMR spectrum, δ, ppm: 10.9, 27.9, 28.9 ($4CH_3$); 38.1, 53.1 ($2CH_2$); 35.3; 121.4; 129.0; 149.0; 167.7; 189.2 (C=O); 195.0 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 220 [M]$^+$ (2), 177 (81), 121 (100), 82 (43), 55 (33), 43 (53). Found, %: C 71.17; H 7.19. $C_{13}H_{16}O_3$. Calculated, %: C 70.89; H 7.32.

**Ethyl 3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (6b)**. Yield 0.38 g (76%), white powder, mp 72–74°C. IR spectrum, ν, cm$^{-1}$ : 2957, 1716, 1672, 1457, 1242, 1144, 766. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (6H, s, $2CH_3$); 1.44 (3H, t, $^3J$ = 7.1, $CH_2C\underline{H}_3$); 2.39 (2H, s, $CH_2$); 2.57 (3H, s, $CH_3$); 2.79 (2H, s, $CH_2$); 4.39 (2H, q, $^3J$ = 7.1, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 10.7, 14.7, 28.8 ($4CH_3$); 38.0, 53.1 ($2CH_2$); 61.3 ($OCH_2$); 35.3; 121.0; 129.9; 140.9; 159.8; 168.3 (C=O); 194.9 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 250 [M]$^+$ (2), 177 (88), 121 (100), 82 (45), 55 (36), 41 (36). Found, %: C 67.27; H 7.20. $C_{14}H_{18}O_4$. Calculated, %: C 67.18; H 7.25.

**Ethyl 3-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (6c)**. Yield 0.32 g (72%), white powder, mp 87–89°C (mp 88–90°C,[4g] mp 93–94°C (ligroin)[16]). IR spectrum, ν, cm$^{-1}$: 2921, 1714, 1674, 1455, 1218, 771. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, $^3J$ = 7.1, $CH_2C\underline{H}_3$); 2.17–2.21 (2H, m, $CH_2$); 2.53 (2H, t, $^3J$ = 6.4, $CH_2$); 2.57 (3H, s, $CH_3$); 2.94 (2H, t, $^3J$ = 6.8, $CH_2$); 4.39 (2H, q, $^3J$ = 7.1, $CH_2O$). $^{13}$C NMR spectrum, δ, ppm: 10.7, 14.7 ($2CH_3$); 22.5, 24.1, 38.8 ($3CH_2$); 61.3 ($OCH_2$); 122.1; 130.1; 140.1; 160.0; 169.0 (C=O); 195.5 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 222 [M]$^+$ (56), 194 (60), 166 (45), 83 (45), 57 (100). Found, %: C 64.89; H 6.30. $C_{12}H_{14}O_4$. Calculated, %: C 64.85; H 6.35.

**2-Acetyl-3-methyl-6,7-dihydrobenzofuran-4(5*H*)-one (6d)**. Yield 0.27 g (71%), white powder, mp 114–116°C. IR spectrum, ν, cm$^{-1}$: 2922, 1734, 1677, 1218, 766. $^1$H NMR spectrum, δ, ppm (*J*, Hz): 2.19–2.21 (2H, m, $CH_2$); 2.42 (3H, s, $CH_3$); 2.47 (2H, t, $^3J$ = 7.5, $CH_2$); 2.50 (3H, s, $CH_3$); 2.97 (2H, t, $^3J$ = 6.0, $CH_2$). $^{13}$C NMR

spectrum, δ, ppm: 9.9, 22.3 ($2CH_3$); 23.6, 26.9, 38.4 ($3CH_3$); 123.1; 128.9; 154.6; 169.2; 188.3 (C=O); 194.0 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 192 $[M]^+$ (53), 149 (64), 71 (53), 57 (100), 43 (75). Found, %: C 68.85; H 6.39. $C_{11}H_{12}O_3$. Calculated, %: C 68.74; H 6.29.

**Ethyl 1,3,5-trimethyl-2,4-dioxo-1,2,3,4-tetrahydrobenzofuro[2,3-*d*]pyrimidine-6-carboxylate (6e)**. Yield 0.37 g (69%), white powder, mp 158–160°C. IR spectrum, ν, $cm^{-1}$: 2924, 1683, 1636, 1344, 770. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, t, $^3J$ = 7.1, $CH_2C\underline{H}_3$); 2.65 (3H, s, $CH_3$); 3.40 (3H, s, $CH_3$); 3.62 (3H, s, $CH_3$); 4.39 (2H, q, $^3J$ = 7.1, $CH_2O$). $^{13}C$ NMR spectrum, δ, ppm: 10.8, 14.7, 28.5, 31.8 ($4CH_3$); 61.5 ($OCH_2$); 131.6, 137.0, 150.9, 156.1 (C Ar); 158.8, 158.9, 170.2 (3C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 266 $[M]^+$ (100), 209 (91), 181 (77), 137 (28), 109 (46), 80 (46). Found, %: C 54.22; H 5.45; N 10.41. $C_{12}H_{14}N_2O_5$. Calculated, %: C 54.13; H 5.30; N 10.52.

**Preparation of open-chain adducts 8a,b** (General method). A mixture of the 1,3-dicarbonyl compound **1b**,**c** (2 mmol) and ammonium acetate (0.14 g, 2 mmol) in EtOH–$H_2O$, 7:3 (3 ml) was stirred at 80°C for about an hour. Then 4'-bromophenacyl bromide (**7**) (0.56 g, 2 mmol) was added to the reaction mixture and the stirring was continued for 3 h. The solvent was removed under reduced pressure, and the viscous residue was purified by column chromatography using hexane–AcOEt, 6:1, as eluent.

**2-[2-(4-Bromophenyl)-2-oxoethoxy]-5,5-dimethylcyclohex-2-enone (8a)**. Yield 0.57 g (85%), white powder, mp 177–179°C (mp 182–183°C[17]). IR spectrum, ν, $cm^{-1}$: 1709, 1601, 1383, 1208. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 1.10 (6H, s, $2CH_3$); 2.23 (2H, s, $CH_2$); 2.44 (2H, s, $CH_2$); 5.10 (2H, s, $CH_2O$); 5.20 (1H, s, CH); 7.65 (2H, d, $^3J$ = 8.5, H Ar); 7.77 (2H, d, $^3J$ = 8.5, H Ar). $^{13}C$ NMR spectrum, δ, ppm: 28.6 ($2CH_3$); 33.0 (C); 42.9, 51.1 ($2CH_2$); 70.2 ($OCH_2$); 102.8 (CH); 129.7; 132.7; 129.9; 133.1; 175.4; 191.3 (C=O); 199.6 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 338 $[M(^{81}Br)]^+$ (19), 336 $[M(^{79}Br)]^+$ (18), 323 $[M(^{81}Br)–CH_3]^+$ (43), 321 $[M(^{79}Br)–CH_3]^+$ (41), 185 $[^{81}BrC_6H_4CO]^+$ (100), 183 $[^{79}BrC_6H_4CO]^+$ (98), 157 (13), 155 (13). Found, %: C 56.88; H 5.16. $C_{16}H_{17}BrO_3$. Calculated, %: C 56.99; H 5.08.

**3-[2-(4-Bromophenyl)-2-oxoethoxy]cyclohex-2-enone (8b)**. Yield 0.34 g (55%), white powder, mp 179–181°C (mp 182–183°C[17]). IR spectrum, ν, $cm^{-1}$: 1701, 1637, 1392, 1222. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 2.00–2.08 (2H, m, $CH_2$); 2.38 (2H, t, $^3J$ = 7.6, $CH_2$); 2.50 (2H, t, $^3J$ = 6.2, $CH_2$); 5.14 (2H, s, $CH_2O$); 5.28 (1H, s, CH); 7.67 (2H, d, $^3J$ = 7.7, H Ar); 7.79 (2H, d, $^3J$ = 7.7, H Ar). $^{13}C$ NMR spectrum, δ, ppm: 21.5, 29.1, 37.1 ($3CH_2$); 70.1 ($OCH_2$); 104.1 (CH); 129.7; 132.8; 130.0; 132.8; 177.2; 191.3 (C=O); 199.8 (C=O). Mass spectrum, *m*/*z* ($I_{rel}$, %): 310 $[M(^{81}Br)]^+$ (25), 308 $[M(^{79}Br)]^+$ (27), 185 $[^{81}BrC_6H_4CO]^+$ (98), 183 $[^{79}BrC_6H_4CO]^+$ (100), 157 (13), 155 (16). Found, %: C 54.29; H 4.32. $C_{14}H_{13}BrO_3$. Calculated, %: C 54.39; H 4.24.

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