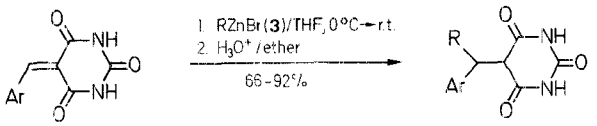
Synthesis of Substituted Barbituric Acids *via* Organozinc Reagents

Y. FRANGIN, C. GUIMBAL, F. WISSOCQ, H. ZAMARLIK*

Laboratoire de Chimie Organique et Biologique, Université François Rabelais, Faculté des Sciences de Tours, Parc de Grandmont, F-37200 Tours, France

5-(1,2-Diarylethyl)- and 5-(1-aryl-3-butenyl)-barbituric acids are prepared in good yields from 5-benzylidenebarbituric acids and benzylzinc bromide or allylzinc bromide, respectively. The products are used as starting materials for the synthesis of the correspondingly 5-substituted 1,3,5-triallyl-, 1,3,5-tris[2-propynyl]-, and 5-hydroxybarbituric acid derivatives.

Various methods for the synthesis of 5-substituted barbituric acid derivatives are known[1-6]. We describe here a simple method for the synthesis of 5-(1,2-diarylethyl)- and 5-(1-aryl-3-butenyl)-barbituric acids (**2**) which consists of the 1,4-addition of benzylzinc bromide or allylzinc bromide (**3**), respectively, to 5-benzylidenebarbituric acids (**1**), followed by hydrolysis.



1 **2a-i**

1, 2	R	Ar
a	$H_2C=CHCH_2$	C_6H_5
b	$H_2C=C(CH_3)CH_2$	C_6H_5
c	$C_6H_5CH_2$	C_6H_6
d	$H_2C=CHCH_2$	$2\text{-}CH_3OC_6H_4$
e	$H_2C=C(CH_3)CH_2$	$2\text{-}CH_3OC_6H_4$
f	$C_6H_5CH_2$	$2\text{-}CH_3OC_6H_4$
g	$H_2C=CHCH_2$	$4\text{-}CH_3OC_6H_4$
h	$H_2C=C(CH_3)CH_2$	$4\text{-}CH_3OC_6H_4$
i	$C_6H_5CH_2$	$4\text{-}CH_3OC_6H_4$

The present work is related to the reaction of Grignard reagents with 1-substituted and 1,3-disubstituted barbituric acids[7]. However, we found that the reaction of benzyl- and allylmagnesium halides (Mg analogs of **3**) with 5-benzyl-

Table. Compounds **2**, **6**, **7**, and **8** Prepared

Product	Yield [%]	m.p.[a]	Molecular Formula[b]	IR[c] (KBr) ν [cm^{-1}]		UV[d] (ethanol) λ_{max} [nm]	^{1}H-NMR ($CDCl_3$/acetone-d_6)[e] δ [ppm]
				NH	C=O		
2a	82	118–120 ($CHCl_3$)	$C_{14}H_{14}N_2O_3$ (258.3)	3245, 3100	1745, 1710, 1690	211, 268	2.93 (t, 2H, $-CH_2-$, ^3J = 7 Hz); 3.70 [m, 2H, $CH-CH(CO)_2$; D_2O: t, 1H, Ar–CH, ^3J = 8 Hz]; 5.0–5.5 (m, 2H, $H_2C=$); 5.6–6.4 (m, 1H, $-CH=$); 7.30 (s, 5H_{arom}); 9.80 (br. s, 2H, 2NH; D_2O: exchange)
2b	66	144–146 ($CHCl_3$)	$C_{15}H_{16}N_2O_3$ (272.3)	3215, 3090	1745, 1690	207, 268	1.80 (s, 3H, CH_3); 2.60 (dd, 1H, CH^1H^2, ^2J = 14.5 Hz, ^3J = 7 Hz); 3.17 (dd, 1H, CH^1H^2, ^2J = 14.5 Hz, ^3J = 9 Hz); 3.70 (d, 1H, CO–CH–CO, ^3J = 3 Hz; D_2O: exchange); 3.90 (m, 1H, Ar–CH; D_2O: dd, ^3J = 7 Hz and 9 Hz); 4.97 (s, 2H, $H_2C=$); 7.32 (s, 5H_{arom}); 9.93 (br. s, 2H, 2NH; D_2O: exchange)
2c	72	98–100 ($CHCl_3$)	$C_{18}H_{16}N_2O_3$ (308.3)	3215, 3100	1750, 1720, 1705, 1690	269	2.8–3.7 (m, 2H, $-CH_2-$); 3.53 (d, 1H, CO–CH–CO, ^3J = 2.5 Hz; D_2O: exchange); 3.8–4.1 (m, 1H, Ar–CH); 7.33 (s, 10H_{arom}); 9.83 (br. s, 2H, 2NH; D_2O: exchange)
2d	76	177–179 ($CHCl_3$)	$C_{15}H_{16}N_2O_4$ (288.3)	3245, 3110	1760, 1705	204, 270	2.83 (m, 2H, $-CH_2-$); 3.70 (d, 1H, CO–CH–CO, ^3J = 3 Hz; D_2O: exchange); 3.83 (s, 3H, OCH_3); 4.13 (td, 1H, Ar–CH, ^3J = 3 Hz, 8 Hz; D_2O: t, ^3J = 8 Hz); 4.9–5.4 (m, 2H, $H_2C=$); 5.5–6.5 (m, 1H, $-CH=$); 7.00, 7.27 (2d, 4H_{arom}, ^3J = 7 Hz); 9.83 (m, 2H, 2NH; D_2O: exchange)
2e	69	189–191 ($CHCl_3$)	$C_{16}H_{18}N_2O_4$ (302.3)	3260, 3230, 3165, 3100	1730, 1710	204, 270	1.77 (s, 3H, CH_3); 2.50 (dd, 1H, CH^1H^2, ^2J = 14.5 Hz, ^3J = 6.5 Hz); 3.00 (dd, 1H, CH^1H^2, ^2J = 14.5 Hz, ^3J = 9.5 Hz); 3.63 (d, 1H, CO–CH–CO, ^3J = 2.5 Hz; D_2O: exchange); 3.80 (s, 3H, OCH_3); 4.27 (m, 1H, Ar–CH; D_2O: dd, ^3J = 6.5 Hz, 9.5 Hz); 4.93 (s, 2H, $H_2C=$); 6.93, 7.23 (2d, 4H_{arom}, ^3J = 7 Hz); 9.70 (m, 2H, 2NH; D_2O: exchange)
2f	78	204–206 (benzene/ethanol 3 : 1)	$C_{19}H_{18}N_2O_4$ (338.3)	3250, 3110	1750, 1730, 1715, 1695	203, 270	2.9–3.8 (m, 2H, $-CH_2-$); 3.53 (d, 1H, CO–CH–CO, ^3J = 2.5 Hz; D_2O: exchange); 3.78 (s, 3H, OCH_3); 4.40 (m, 1H, Ar–CH; D_2O: dd, ^3J = 7 Hz, 9 Hz); 6.7–7.6 (m, 9H_{arom}); 9.83 (br. s, 2H, 2NH; D_2O: exchange)
2g	69	140–142 ($CHCl_3$/CCl_4 1 : 1)	$C_{15}H_{16}N_2O_4$ (288.3)	3215, 3110	1730, 1705, 1690	207, 229, 269	2.93 (t, 2H, $-CH_2-$, ^3J = 7.5 Hz); 3.70 [m, 2H, $CH-CH(CO)_2$; D_2O: t, 1H, ArCH, ^3J = 7.5 Hz); 3.80 (s, 3H, OCH_3); 5.0–5.5 (m, 2H, $H_2C=$); 5.6–6.4 (m, 1H, $-CH=$); 6.87, 7.20 (2d, 4H_{arom}, ^3J = 9 Hz); 7.13 (m, 2H, 2NH; D_2O: exchange)
2h	73	159–161 ($CHCl_3$)	$C_{16}H_{18}N_2O_4$ (302.3)	3235, 3085	1715, 1690	204, 224, 269	1.77 (s, 3H, CH_3); 2.53 (dd, 1H, CH^1H^2, ^2J = 14 Hz, ^3J = 7 Hz); 3.10 (dd, 1H, CH^1H^2, ^2J = 14 Hz, ^3J = 9 Hz); 3.63 (d, 1H, CO–CH–CO, ^3J = 3 Hz; D_2O: exchange); 3.80 (s, 3H, OCH_3); 3.5–4.0 (m, 1H, Ar–CH); 4.95 (s, 2H, $H_2C=$); 6.87, 7.20 (2d, 4H_{arom}, ^3J = 9 Hz); 9.93 (m, 2H, 2NH; D_2O: exchange)

Table. (continued)

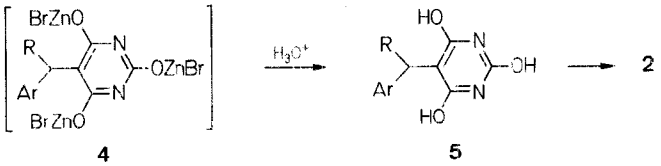
Product	Yield [%]	m.p.[a]	Molecular Formula[b]	IR[c] (KBr) ν [cm^{-1}]		UV[d] (ethanol) λ_{max} [nm]	^{1}H-NMR ($CDCl_3$/acetone-d_6)[e] δ [ppm]
				NH	C=O		
2i	92	138–140 (ethanol/water 1:1)	$C_{19}H_{18}N_2C_4$ (338.3)	3195, 3070	1760, 1705, 1690, 1675	204, 268	2.9–4.15 (m, 3H, CH_2–CH); 3.47 (d, 1H, CO–CH–CO, ^3J = 2.5 Hz; D_2O: exchange); 3.73 (s, 3H, OCH_3); 6.80, 7.20 (2d, 4H_{arom}, ^3J = 9 Hz); 7.40 (m, 5H_{arom}); 8.57 (br. s, 2H, 2NH; D_2O: exchange)
6c	82	wax	$C_{27}H_{28}N_2O_3$ (428.5)		1750[f], 1695	205, 272	2.6–3.8 (m, 5H, CH_2–CH–C–CH_2–C); 4.17, 4.43 (2d, 4H, 2N–CH_2–C, ^3J = 5 Hz); 4.8–6.4 (m, 9H, 3H_2C=CH–); 7.17 (m, 10H_{arom})
6f	50	wax	$C_{28}H_{30}N_2O_4$ (458.5)		1750[g], 1685	204, 278	2.6–3.5 [m, 4H, CH_2–C_6H_5 +, C–CH_2–C(CO)$_2$]; 3.63 (s, 3H, OCH_3); 3.0–4.5 (hidden, 1H, Ar–CH); 4.23, 4.50 (2d, 4H, 2N–CH_2–C, ^3J = 5.5 Hz); 4.8–6.4 (m, 9H, 3H_2C=CH); 6.7–7.5 (m, 9H_{arom})
7a	57	121–123 (ethanol)	$C_{23}H_{20}N_2O_3$ (372.4)		1750[h], 1695	205, 263	1.97, 2.13, 2.30 (3t, 3H, 3HC≡, ^4J = 2.5 Hz); 2.73 (t, 2H, CH_2–C≡, ^3J = 7 Hz); 2.97, 3.13 [2d, 2H, ≡C–CH_2–C(CO)$_2$, ^2J = 9 Hz, ^4J = 2.5 Hz]; 3.40 (t, 1H, Ar–CH, ^3J = 8 Hz); 4.40, 4.67 (2d, 4H, 2N–CH_2–C≡, ^4J = 2.5 Hz); 4.8–5.3 (m, 2H, H_2C=); 5.3–6.6 (m, 1H, –CH=); 7.30 (m, 5H_{arom})
8c	63	238–240 (benzene/ethanol 2:1)	$C_{18}H_{16}N_2O_4$ (324.3)	3245, 3195, 3085	1725[i], 1695	207, 253	3.3–4.0 (m, 3H, CH_2–CH); 5.38 (s, 1H, OH; D_2O: exchange); 7.17 (s, 5H_{arom}); 7.30 (s, 5H_{arom}); 10.10 (m, 2H, 2NH; D_2O: exchange)
8i	60	264–266 (benzene/ethanol 1:1)	$C_{19}H_{18}N_2O_5$ (354.3)	3215, 3105	1765[j], 1715, 1695	204, 270	3.2–3.7 (m, 3H, CH_2–CH); 3.74 (s, 3H, OCH_3); 5.33 (s, 1H, OH; D_2O: exchange); 6.7–7.4 (m, 9H_{arom}); 10.10 (br. s, 2H, 2NH; D_2O: exchange)

[a] Melting points are uncorrected.
[b] All products gave satisfactory analyses: C ±0.3, H ±0.2, N ±0.3.
[c] All IR spectra were recorded on a Beckman Acculab 2 spectrometer.
[d] All UV spectra were recorded on a Varian 634 spectrometer.
[e] All ^{1}H-NMR spectra were recorded on a Varian EM 360 spectrometer at 60 MHz.
[f] IR ν = 1640 cm^{-1} (C=C).
[g] IR ν = 1645 cm^{-1} (C=C).
[h] IR ν = 2140 (C≡C); 3290 cm^{-1} (≡C–H).
[i] IR ν = 3435, 3605 cm^{-1} (OH).
[j] IR ν = 3435 cm^{-1} (OH).

idenebarbituric acids (**1**) affords only 10–15% yields of the desired products **2** whereas the same reaction with the likewise readily accessible organozinc reagents **3** gives products **2** in high yields.

In the UV spectra, compounds **2** do not show the absorption band of the conjugated system of educts **1** (λ_{max} = 326 nm for Ar = C_6H_5, and λ_{max} = 375 nm for Ar = CH_3O–C_6H_4) which confirms saturation of the conjugated exocyclic double bond of **1**.

The organozinc reagents **3** also undergo hydrogen-metal exchange with both NH sites of the substrates **1** as proven by the evolution of propene in the reactions with allylzinc bromide. The reactions therefore lead to approximately quantitative yields of products **2** only if three molecular equivalents or organozinc reagents **3** are employed. An IR study of the reaction mixture in tetrahydrofuran shows the almost complete disappearance of the characteristic bands of the 5-benzylidenebarbituric acids **1** [ν = 3200, 3100 (NH); 1750, 1690 (C=O) cm^{-1}][8,9]. The spectral data suggest the formation of an intermediate **4** from which the tautomer **5** of product **2** is released by acid hydrolysis.

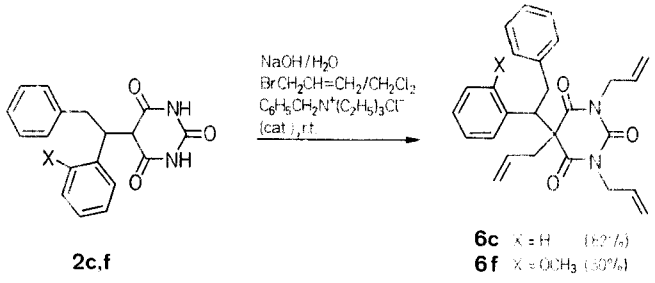


4 **5**

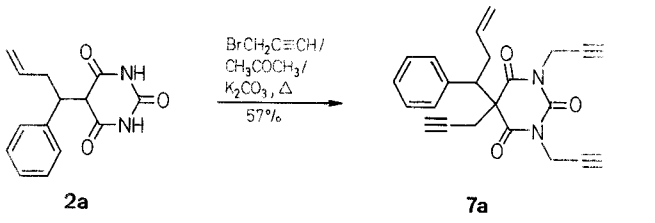
The purification of products **2** utilizes their solubility in aqueous sodium hydroxide from which they are precipitated by acid. They are then dissolved in ether from which they are

isolated and recrystallized from chloroform or other solvents or solvent mixtures (for polymorphism of barbituric acid derivatives, see Lit.[10]).

Various 5,5-disubstituted barbituric acid derivatives are well known for their pharmacological properties[1-2]. The ease with which the barbituric acids **2** may be prepared renders them particularly useful as starting materials for the synthesis of other barbituric acid derivatives. Thus, compounds **2** react with allyl bromide/base under phase-transfer catalysis to give the corresponding 5-substituted 1,3,5-triallylbarbituric acid derivatives (e.g., **6c** and **6f**).

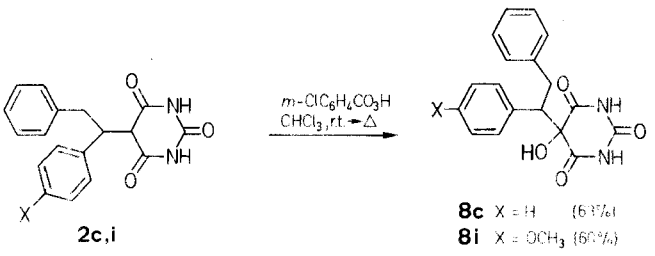


We also prepared barbituric acid **7a** by the known method of Lit.[12]



The same method was used to methylate barbituric acids **2** for capillary GLC analysis.

When barbituric acids **2c** and **2i** were submitted to the reaction with 3-chloroperbenzoic acid the 5-hydroxy derivatives **8c** and **8i**, respectively, were obtained.



To our knowledge, the barbituric acid derivatives listed in the Table are all new compounds. The structures of all products were confirmed by microanalyses, IR-, UV-, and ^{1}H-NMR spectrometry.

The 5-benzylidenebarbituric acids **1** are obtained as described in Lit.[13]. The organozinc reagents **3** are prepared according to Lit.[14,15].

5-(1,2-Diarylethyl)-barbituric Acids (2); General Procedure:

A solution of the allyl- or benzylzinc bromide (**3**; 50 mmol) in tetrahydrofurane is cooled at 0 °C and the 5-benzylidenebarbituric acid (**1**; 12.5 mmol) is added with stirring and cooling. The temperature of the mixture quickly rises to 30 °C; when it begins to fall the cooling bath is removed and stirring is continued at room temperature for 1 h. The mixture is then poured into a mixture of crushed ice (30 g) and conc. hydrochloric acid (5 ml) and ether (20 ml) is added. The phases are separated and the aqueous layer is extracted with ether (4 × 20 ml). The combined organic phase is washed with saturated sodium chloride solution (50 ml), dried with sodium sulfate, and evaporated to give the crude solid product **2**. For purification, the crude product is dissolved in aqueous ~2 normal sodium hydroxide (40 ml), the aqueous layer is washed with ether (40 ml), and strong hydrochloric acid (10 ml) is added to precipitate the product **2**. This product is dissolved in ether (~120 ml), washed with saturated sodium chloride solution (4 × 20 ml), dried with sodium sulfate, and evaporated. The residue is recrystallized from chloroform. Product **2g** is recrystallized from chloroform/tetrachloromethane (1:1). Product **2i** is first dissolved in hot water/ethanol (1:1, ~20 ml), and this solution allowed to cool. The precipitated crystals, which tend to agglomerate, are isolated by suction and dissolved in chloroform (~10 ml); product **2i** is precipitated by the addition of hexane.

TLC analyses of the above mixtures and products **2** are performed on silica gel 60 F_{254} using chloroform/acetone (1:1) as eluent.

1,3,5-Triallyl-5-(1,2-diarylethyl)-2,4,6-trioxohexahydropyrimidines 6c or 6f (cf. Lit.[11]):

5-(1,2-Diphenylethyl)-barbituric acid (**2c**; 1.55 g, 5 mmol) or 5-[1-(2-methoxyphenyl)-1-phenylethyl]-barbituric acid (**2f**; 1.7 g, 5 mmol) is dissolved in a solution of sodium hydroxide (1.2 g, 30 mmol) in water (25 ml). To this solution, benzyltriethylammonium chloride (60 mg, 0.25 mmol) and a solution of allyl bromide (3.6 g, 30 mmol) in dichloromethane (25 ml) are added with stirring (48 h at r.t.). The organic layer is evaporated. The residue is mixed with water (50 ml) and extracted with ether (5 × 20 ml). The ethereal layer is washed with aqueous 2 normal sodium hydroxide (2 × 10 ml), then with saturated sodium chloride solution (4 × 20 ml) and dried with sodium sulfate to give the product **6** as a wax; yield of **6c**: 1.75 g (82%); yield of **6f**: 1.15 g (50%).

5-(1-Phenyl-3-butenyl)-1,3,5-tris[2-propynyl]-2,4,6-trioxohexahydropyrimidine (7a) (cf. Lit.[12]):

5-(1-Phenyl-3-butenyl)-barbituric acid (**2a**; 1.3 g, 5 mmol) and 3-bromopropyne (propargyl bromide; 2.4 g, 20 mmol) are dissolved in acetone (10 ml) and potassium carbonate (2.75 g) is added with stirring (reflux 48 h). The organic layer is filtered and evaporated. The residue is mixed with water (50 ml) and extracted with ether (5 × 10 ml). The ethereal layer is treated with aqueous 2 normal sodium hydroxide (2 × 10 ml), washed with saturated sodium chloride solution (4 × 20 ml) and dried with sodium sulfate, then evaporated. The residue is recrystallized from absolute ethanol; yield: 1.06 g (57%).

Capillary Gas Chromatography of Barbituric Acid Derivatives 2:

5-Substituted 1,3,5-Trimethyl-2,4,6-trioxohexahydropyrimidines:

Methyl iodide (1 ml) and potassium carbonate (1 g) are added to a solution of the barbituric acid **2** (100 mg) in acetone (2 ml). The mixture is stirred at reflux for 15 h. Then, the organic layer is filtered and evaporated. The residue is mixed with water (20 ml) and extracted with ether (4 × 5 ml). The ethereal layer is washed with aqueous 2 normal sodium hydroxide (2 × 5 ml), washed with saturated sodium chloride solution (4 × 5 ml) and dried with sodium sulfate.

Capillary GLC: A 1‰ solution of the methyl derivative of **2** in ether is used.

Intersmat Chromatograph IGC 121C.

Capillary column: WCOT fused silica 25 m × 0.33 mm.

CP Wax 51, nitrogen as carrier gas (0.7 bar).

Injection "on column" at 30 °C.

Temperature program: 200 to 250 °C (10 °/min). FID (H_2) 250 °C.

5-Hydroxy-5-(1,2-diarylethyl)-barbituric Acids 8c or 8i:

5-(1,2-Diphenylethyl)-barbituric acid (**2c**; 1.55 g, 5 mmol) or 5-[1-(4-methoxyphenyl)-1-phenylethyl]-barbituric acid (**2i**; 1.7 g, 5 mmol) and 3-chloroperbenzoic acid (2.65 g, 15.5 mmol) are added to chloroform (110 ml). This mixture is stirred at room temperature overnight, then on a boiling water bath for 1 h. After cooling, the precipitated product **8c** or **8i** is isolated by suction and recrystallized from benzene/ethanol; yield of **8c**: 1.02 g (63%); yield of **8i**: 1.06 g (60%).

Received: January 17, 1986
(Revised form: May 5, 1986)

[1] Kaufmann, H.P. *Médicaments de Synthèse, Masson & Cie, Paris 1957, p. 35.*
[2] Burger, A. *Medicinal Chemistry*, 3rd. Ed., Wiley-Interscience, New York, 1970, p. 1367.
[3] Dzhumageldyeva, N., Konkova, V.A., Verkhodanova, N. *Zh. Prikl. Khim.* **1966**, *39*, 483; *C.A.* **1966**, *64*, 15877.
[4] Makoto, F., Yoshiyasu, T., Minoru, S. *Chem. Pharm. Bull.* **1974**, *22*, 2675.
[5] Otto, H.H., Triepel, J. *Liebigs Ann. Chem.* **1976**, 1982.
[6] Sokovishina, I.F., Perekalin, V.V. *Zh. Org. Khim.* **1978**, *14*, 1817; *C.A.* **1978**, *89*, 214462.
[7] Shalaby, A.F.A., Abd El-Gawad, I.I. *J. Prakt. Chem.* **1971**, *313*, 1022.
[8] Goenechea, S. *Z. Anal. Chem.* **1966**, *218*, 416.
[9] Bouche, R. *Chim. Thér.* **1973**, *8*, 676.
[10] Nikolics, K., Bidlo, G., Nikolics, Mrs. K. *Acta Pharm. Hung.* **1974**, *44*, 133.
[11] Hedayatullah, M. *Synth. Commun.* **1982**, *12*, 565.
[12] Danielsson, *Acta Pharm. Suec.* **1965**, *2*, 47.
[13] Speer, H., Dabovich, T.C. *Org. Synth. Coll. Vol.* III, **1955**, 39.
[14] Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974.
[15] Bellassoued, M., Frangin, Y. *Synthesis* **1978**, 838.