Pergamon

Tetrahedron Letters 42 (2001) 4103–4107

TETRAHEDRON LETTERS

Reductive *C*-alkylation of barbituric acid derivatives with carbonyl compounds in the presence of platinum and palladium catalysts†

Branko S. Jursic* and Donna M. Neumann

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

Received 26 February 2001; revised 9 April 2001; accepted 10 April 2001

Abstract—Effective synthetic procedures for the preparation of mono- and di-*C*-alkylated barbituric acid derivatives through palladium and platinum catalytic hydrogenation of solutions of barbituric acids (unsubstituted, *N*-mono, and *N*,*N*′-disubstituted barbituric acids) and carbonyl compounds (aliphatic and aromatic aldehydes and ketones).

The list of biologically active substituted barbituric acids is very long;[1] therefore, there is no surprise that since the first synthesis research[2] in this field, the synthesis and applications of these compounds have only increased with time. Pharmaceutical industries market many of these compounds under various commercial names. The majority of barbituric acids are single or double *C*-alkylated barbituric acids. Barbituric acid by itself (pyrimidine-2,4,6-trione) is an inexpensive commercially available starting material, and the same is true for 1-mono (*N*-substituted) and 1,3-substituted (*N*,*N*′-disubstituted) barbituric acids. It is obvious that these compounds should be ideal starting materials for both laboratory and industrial preparation of *C*-alkylated barbituric acid derivatives. Surprisingly, however, there is not a simple general synthetic procedure for the preparation of mono- and *C*-alkylated barbituric acid derivatives. The general route for their preparation is through the condensation of urea and malonic ester derivatives with sodium ethoxide in ethanol.[3]

Currently barbiturates have been used predominantly for their anticonvulsant and sedative–hypnotic properties. Phenobarbital, the oldest of the commonly used barbiturates, was first used as an anticonvulsant in 1911.[4] It was regularly prescribed to prevent febrile seizures in infants, but is now infrequently used for this due to side effects and lack of efficiency. In pediatrics, phenobarbital is still used as a single agent, but in adults, phenobarbital is considered a third- or fourth-line anticonvulsant and is frequently administered in combination with other agents. Generally, barbiturates are somewhat effective in all seizure disorders, except in absence (petit mal) seizures.[5]

Here, we would like to present several catalytic reductive alkylation procedures for the preparation of mono- and di-*C*-alkylated barbituric acid derivatives. Although our procedures are general and almost all 5-alkyl- or 5,5-dialkyl-derivatives can be prepared, many of the reactions required different solvents, catalysts and order of the reactants mixing. The best catalysts for these reactions are palladium, 5 wt% (dry basis) on active carbon with the water content normally 50%, and platinum, 5 wt% (dry basis) on active carbon with the water content normally 50%. By combining these catalysts together with a specific order of adding the reactants into the reaction mixture, as well as the solvent selection, the selective mono- and di-*C*-alkylations of three classes of barbituric acids were achieved, using barbituric acid as the unsubstituted barbituric acid, 1-phenylbarbituric acid as *N*-substituted acid, and 1,3-dimethylbarbituric acid as *N*,*N*′-disubstituted barbituric acid.

It is possible to selectively perform mono-*C*-alkylation of barbituric acids with aliphatic aldehydes and ketones under catalytic reductive alkylation conditions.[6] The first step in the reductive alkylation is the formation of the Knoevenagel condensation product,[7] followed by catalytic reduction of the newly formed C=C double

* Corresponding author.

† All reactions presented in this paper are part of a pending US Patent.

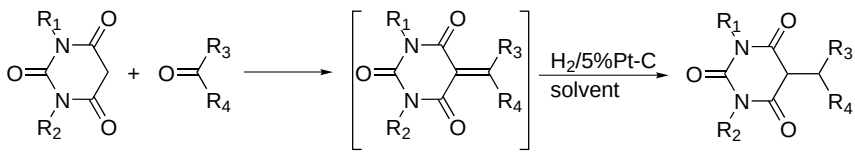
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00621-9

bond (Table 1). The condensation reaction is catalyzed by acid. Barbituric acid by itself is an acid and if one or both R_1 and R_2 are hydrogens then the condensation reaction can be carried in solvents such as methanol or ethanol. With aliphatic aldehydes and ketones, the reduction can be carried out immediately upon condensation, making the reaction a one-pot synthesis. In some instances when the carbonyl compound is also the solvent (acetone), the reaction can be carried out in large molar excesses of the carbonyl compound. Even in these cases, only the mono-*C*-alkylation product of the barbituric acid was isolated. Both aliphatic ketones and aldehydes are good alkylating agents and there is no restriction on the structure of the carbonyl compounds, with the exception of compounds with reductive hydrogenation-sensitive functionalities. If both R_1 and R_2 are not hydrogens, then acidic conditions are required for the reaction to proceed. Acetic acid, with a few drops of sulfuric acid, seems to be sufficient to catalyze the condensation reactions.

Mono-*C*-benzylation of barbituric acid with aromatic aldehydes seems to be a particularly straightforward procedure that affords *C*-benzylated barbituric acids in high yields (Table 2). If the monoalkylated product is to be synthesized the reaction has to be carried out in two steps: the first being to produce the product of the Knoevenagel condensation and the second being the reduction of this product into the substituted benzylbarbituric acid. Extended conjugation on the aromatic aldehyde, or electron-donating groups such as methoxy and dimethylamino, substantially decrease the reaction time. For instance, the condensation between barbituric acid and 4-dimethylaminobenzaldehyde in hot methanol is completed in several seconds. Therefore, the catalytic reduction can be carried out in the same reaction mixture without isolation of the condensation product. Conjugated double bonds of the condensation product (Table 2) hydrogenate first, but both platinum and palladium catalysts are capable of reducing the aromatic ring with electron-donating groups such as methoxy and dimethylamino. Reduction of the double conjugated double bond is practically over in 1–2 h. If the reaction is stopped at this point the reaction mixture will also contain the product of the aromatic reduction. Adding into the reductive solution a small amount of 4-methoxybenzyl alcohol can solve this problem. It was demonstrated that arylidenebarbituric acid derivatives, under mild conditions, might be reduced to the corresponding benzylbarbituric acid with allylic and benzylic alcohols.[8] Through further experiments, we have demonstrated that benzene as solvent reduces or totally eliminates the aromatic ring reduction. Therefore, when benzene is used as a co-solvent the only product isolated is the pure, mono-*C*-benzylated barbituric acid derivative.[9]

With reactive aromatic or conjugated aldehydes the double benzylation of barbituric acid is possible. In this case, it seems that a 50% excess of the aromatic aldehyde also serves as an inhibitor to stop further reduction, as seen with the previous examples using benzene. Isolation of the product is simple and the yields of double benzylation are very high (Table 3). If the reaction is performed with a barbituric acid that is sufficiently acidic enough to catalyze the condensation reaction, the addition of sulfuric acid is not necessary. In other cases, such as reactions with 1,3-dimethylbar-

Table 1. Reductive alkylation of barbituric acid derivatives with aliphatic ketones and aldehydes

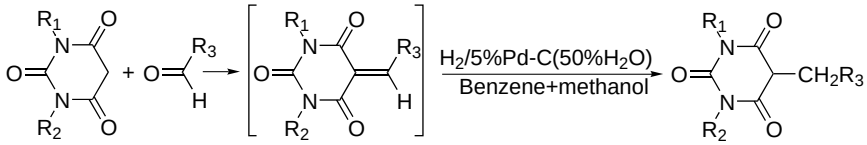


Entry	R_1	R_2	R_3	R_4	Solvent	Yield (%)
1	H	H	H	H	Methanol[a]	83
2	H	H	*n*-C_6H_7	H	Methanol[a]	97
3	H	H	*n*-$C_{11}H_{23}$	H	Methanol[a]	95
4	H	H	-$(CH_2)_5$-		Methanol[a]	95
5	H	H	CH_3	CH_3	Methanol[a]	98
6	H	H	CH_3	*n*-C_6H_5	Methanol[a]	93
7	H	C_6H_5	H	H	Acetic acid	92
8	H	C_6H_5	*n*-C_6H_{13}	H	Acetic acid	92
9	H	C_6H_5	-$(CH_2)_5$-		Acetic acid	95
10	H	C_6H_5	CH_3	CH_3	Acetic acid	96
11	CH_3	CH_3	H	H	Acetic acid[b]	93
12	CH_3	CH_3	*n*-C_6H_7	H	Acetic acid[b]	93
13	CH_3	CH_3	CH_3	CH_3	Acetic acid[b]	97
14	CH_3	CH_3	CH_3	*n*-C_6H_{13}	Acetic acid[b]	91
15	CH_3	CH_3	-$(CH_2)_5$-		Acetic acid[b]	91

[a] The product was isolated by separation of catalyst by filtration, concentrating the filtrate to 1/10 volume and precipitation of product by dilution with water.

[b] A few drops of concentrated sulfuric acid were added into the reaction suspension prior to hydrogenation.

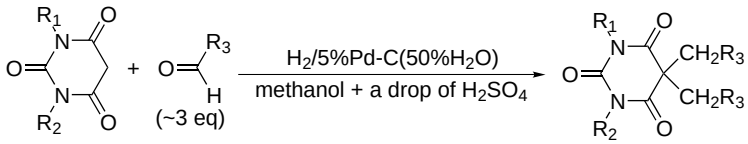
Table 2. Monoreductive benzylation with aromatic aldehydes



Entry	R_1	R_2	R_3	Yield (%)
1	H	H	C_6H_5	85
2	H	H	2-Naphthyl	90
3	H	H	*m*-$CH_3OC_6H_4$	93
4	H	H	*p*-$CH_3C_6H_4$	95
5	H	H	*o*-$CH_3OC_6H_4$	92
6	H	H	*m*-$CH_3OC_6H_4$	94
7	H	H	*p*-$CH_3OC_6H_4$	95
8	H	H	*p*-$(CH_3)_2NC_6H_4$	97
9	H	H	$C_6H_5CH{=}CH$[a]	92
10	H	H	*p*-$(CH_3)_2NC_6H_4CH{=}CH$[a]	89
11	H	H	3-Indoyl	92
12	C_6H_5	H	C_6H_5	94
13	C_6H_5	H	*p*-$CH_3C_6H_4$	91
14	C_6H_5	H	*p*-$CH_3OC_6H_4$	93
15	C_6H_5	H	*p*-$(CH_3)_2NC_6H_4$	96
16	C_6H_5	H	3-Indoyl	97
17	CH_3	CH_3	C_6H_5	88
18	CH_3	CH_3	*p*-$CH_3C_6H_4$	93
19	CH_3	CH_3	*p*-$CH_3OC_6H_4$	91
20	CH_3	CH_3	*p*-$(CH_3)_2NC_6H_4$	97
21	CH_3	CH_3	$C_6H_5CH{=}CH$[a]	91
22	CH_3	CH_3	*p*-$(CH_3)_2NC_6H_4CH{=}CH$[a]	94
23	CH_3	CH_3	3-Indoyl	95

[a] In the product, the conjugated double bond is hydrogenated (CH=CH is replaced with CH_2CH_2).

Table 3. Symmetric, double benzylation with aromatic and conjugated aldehydes



Entry	R_1	R_2	R_3	Yield (%)
1	H	H	C_6H_5	86
2	H	H	*p*-$CH_3C_6H_4$	91
3	H	H	*p*-$CH_3OC_6H_4$	95
4	H	H	*p*-$(CH_3)_2NC_6H_4$	95
5	H	H	$C_6H_5CH{=}CH$[a]	94
6	H	H	*p*-$(CH_3)_2NC_6H_4CH{=}CH$[a]	95
7	H	C_6H_5	*p*-$CH_3OC_6H_4$	91
8	H	C_6H_5	*p*-$(CH_3)_2NC_6H_4$	94
9	CH_3	CH_3	*p*-$CH_3OC_6H_4$	93
10	CH_3	CH_3	*p*-$(CH_3)_2NC_6H_4$	92

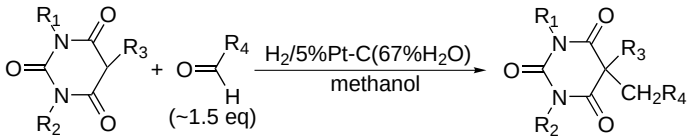
[a] The conjugated double bond is reduced in the product.

bituric acid, a few drops of sulfuric acid substantially facilitates the reaction.[10]

C-Benzylation can also be performed on *C*-monoalkylated barbituric acids through reductive alkylation with activated aromatic aldehydes.[11] Unfortunately, the second alkylation with aliphatic aldehydes and ketones was not successful unless the alkylation was performed with activated, unsaturated aldehydes, such as 4-dimethylaminocinnamaldehyde (Table 4).

It was demonstrated that through catalytic reductive alkylation, various derivatives of barbituric acids can be prepared in almost quantitative yields from simple, readily available barbituric acids and aldehydes and ketones. If carbonyl compounds are aliphatic then only

Table 4. Second reductive alkylation with activated unsaturated and aromatic aldehydes



Entry	R_1	R_2	R_3	R_4	Yield (%)
1	H	H	$CH(CH_3)_2$	C_6H_5	75
2	H	H	$CH(CH_3)_2$	p-$CH_3C_6H_4$	83
3	H	H	$CH(CH_3)_2$	p-$CH_3OC_6H_4$	87
4	H	H	$CH(CH_3)_2$	p-$(CH_3)_2NC_6H_4$	85
5	H	H	$C_6H_5(CH_2)_3$	p-$(CH_3)_2NC_6H_4$	79
6	H	H	$C_6H_5(CH_2)_3$	p-$(CH_3)_2NC_6H_4CH{=}CH$[a]	89
7	H	C_6H_5	$CH(CH_3)_2$	p-$CH_3OC_6H_4$	85
8	H	C_6H_5	$CH(CH_3)_2$	p-$(CH_3)_2NC_6H_4$	87
9	H	C_6H_5	$CH(CH_3)_2$	p-$(CH_3)_2NC_6H_4CH{=}CH$[a]	92

[a] The conjugated double bond is reduced in the product.

the single *C*-alkylation is possible, while with activated aromatic or conjugated aldehydes, both single and double alkylation can also be achieved. If asymmetric double alkylation is to be achieved, first the simple alkylation with aliphatic aldehydes should be performed, followed by the reductive alkylation with conjugated or aromatic aldehydes. All of these reactions can be achieved without isolation of intermediates (one-pot synthesis).

References

1. For instance, see: Smith, C. M.; Reynard, A. M. *Essentials of Pharmacology*; W. B. Sanders: Philadelphia, 1995.
2. For an historical account of barbituric acids, see: (a) Carter, M. K. *J. Chem. Ed.* **1951**, *28*, 524. For the preparation of barbital by the condensation of the diethyl ester of diethylmalonic acid with urea in sodium ethoxide solution, see: (b) Fischer, Dilthey, *Ann.* **1904**, *335*, 334; German Patent No. 146,497, 1903. For early therapeutic work, see: (c) Fischer, V. M. *Therapeutische Monatsh.* **1903**, *17*, 208.
3. For instance, see: (a) *A Textbook of Practical Organic Chemistry (Vogel)*, 3rd ed.; Wiley: New York, 1966; p. 1001; (b) Weygand/Hilgetag *Preparative Organic Chemistry*; Wiley: New York, 1972; p. 493; (c) Dickey, J. B.; Gray, A. R. *Org. Syn. Coll. Vol. II* **1943**, 60; (d) Beres, J. A.; Pearson, D. E.; Bush, M. T. *J. Med. Chem.* **1967**, *10*, 1078.
4. For preparation, see: (a) German Patent No. 247,952, 1911 (Bayer Pharmaceutical Co.). Also see: (b) Pinhey, J. T.; Rowe, B. A. *Tetrahedron Lett.* **1980**, *21*, 965. For toxicity, see: (c) Goldenthal, *Toxicol. Appl. Pharmacol.* **1971**, *18*, 185.
5. For a general review of barbituric acids, see: (a) *Burger's Medical Chemistry and Drug Discovery: Therapeutical Agents*, 5th ed.; Wolff, M. E., Ed.; Wiley: New York, 1997; Vol. II–V; (b) Goth, A. *Medical Pharmacology*, 4th ed.; The Mosby Company: St. Louis, MN, 1968.
6. **Typical procedure for mono-*C*-alkylation with aliphatic aldehydes and ketones**: Preparation of 5-isopropyl-1-phenylbarbituric acid. A suspension of 1-phenylbarbituric acid (2.04 g, 10 mmol) and 5% Pt–C with 50% water (0.2 g) in acetone (30 mL) and acetic acid (100 mL) was hydrogenated under a hydrogen pressure of 50 psi for ~20 h. The catalyst was separated by filtration, the filtrate was evaporated to an oily residue and benzene (3×50 mL) was added successively and evaporated to eliminate residue of acetic acid to give racemic 5-isopropyl-1-phenylbarbituric acid (2.35 g, 96%). ^{1}H NMR (DMSO-d_6): δ 11.583 (1H, s, NH), 7.435 (3H, m), 7.220 (2H, d, J=8.1), 3.410 (1H, d, J=3.9), 2.480 (1H, m), 1.080 (6H, 2d, J=5.7); ^{13}C NMR (DMSO-d_6): δ 165.662, 165.473, 147.374, 131.278, 1.25.292, 125.262, 125.160, 124.774, 124.636, 51.302, 28.848, 16.008, 15.957; MS (EI): m/z 69 (40%, $CH_3CH{=}CHCO^+$), 77 (5%, $C_6H_5^+$), 83 (40%, $(CH_3)_2C{=}CHCO^+$), 91, 119 (80%, $PhN{=}C{=}O^+$), 176 (25%, $PhNHCOCH_2CONH_2^+$), 204 (100%, $M{-}C(CH_3)_2^+$), 231 (20%, $M{-}CH_3^+$), 246 (20%, M^+), 247 (2%, M^++1). Anal. calcd for $C_{13}H_{14}N_2O_3$ (FW 246.26): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.21; H, 5.92; N, 11.14.
7. Recently, we have published preparation of the Knoevenagel condensation products for aromatic aldehydes: Jursic, B. S. *J. Heterocyclic Chem.*, in press.
8. Tanaka, K.; Chen, X.; Kimura, T.; Yoneda, F. *Chem. Pharm. Bull.* **1988**, *36*, 60.
9. **Typical procedure for reductive benzylation with aromatic aldehydes**: Preparation of 5-naphthalen-2-ylmethylbarbituric acid. Barbituric acid (1.28 g, 10 mmol) and 2-naphthaldehyde (1.56 g, 10 mmol) was refluxed in methanol (100 mL) for 30 min. The reaction suspension was cooled to room temperature and 5% Pd–C with 50% water (0.1 g) was added, together with benzene (50 mL) and hydrogenated at 30 psi for 4 h. The catalyst was separated by filtration and the solvent was evaporated to a solid residue. The solid residue was dissolved in methanol (~10 mL) and diluted with water (300 mL). The white precipitate was separated by filtration and dried in air to give 5-naphthalen-2-ylmethylbarbituric acid (2.4 g, 90%). ^{1}H NMR (DMSO-d_6): δ 11.151 (1H, s, NH), 8.138 (1H, d, J=6.6), 7.899 (1H, d, J=6.6), 7.71 (1H, d, J=8.7), 7.517 (2H, m), 7.412 (1H, t, J=7.5), 7.254 (1H, d,

$J=6.6$), 3.959 (1H, t, $J=6.6$), 3.668 (2H, d, $J=6.6$); ^{13}C NMR (DMSO-d_6): δ 166.017, 146.607, 130.271, 129.251, 127.416, 124.437, 122.922, 122.558, 44.862, 25.933; MS (CI): m/z 91 ($C_7H_7^+$), 115 (12%, $C_8H_9^+$), 128 (17%, barbituric acid), 129 (16%, $C_{10}H_9^+$), 141 (100%, $C_{11}H_{10}^+$), 169 (7%, $C_{11}H_{10}CO^+$), 268 (45%, M^+), 269 (10%, M^++1). Anal. calcd for $C_{16}H_{12}N_2O_3$ (FW 268.27): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.01; H, 4.82; N, 10.08.

10. **Typical procedure for symmetric double reductive benzylation of barbituric acid**: Preparation of 5,5-di(4-dimethylaminobenzyl)barbituric acid. A mixture of barbituric acid (0.64 g, 0.005 mol) and 4-dimethylaminobenzaldehyde (2.44 g, 15 mmol) in methanol (100 mL) was refluxed for ~15 min. The reaction mixture changed from a suspension (low solubility of barbituric acid) to a clear solution followed by a new suspension. Into this suspension 5% Pd–C with 50% water (0.150 g) was added and the suspension was hydrogenated at 30 psi at room temperature overnight (~14 h). The catalyst was separated by filtration and methanol was evaporated to a reduced volume (10 mL). Water was added (~100 mL) and the resulting solid was separated by filtration and washed with CCl_4 (3×50 mL), and dried in air to give 5,5-di(4-dimethylaminobenzyl)barbituric acid (1.87 g, 95%). The product decomposed at temperatures above 230°C. ^{1}H NMR (DMSO-d_6): δ 11.092 (2H, s, NH), 6.840 (4H, d, $J=8.7$, Ar), 6.572 (4H, d, $J=8.7$, Ar), 3.103 (4H, s, CH_2), 2.816 (12H, s, CH_3); ^{13}C NMR (DMSO-d_6): δ 169, 145, 145, 126, 118, 108, 56, 39, 36; MS (EI): m/z 134 (100%, $N(CH_3)_2C_6H_4CH_2^+$), 261 (12%, M–$CH_2C_6H_5N(CH_3)_2$+1$^+$), 394 (48%, M^+). Anal. calcd for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.55; H, 6.85; N, 13.97.

11. **Typical procedure for reductive benzylation of *C*-substituted barbituric acid**: Preparation of 5-(4-dimethylaminobenzyl)-5-(3-phenylpropyl)barbituric acid. A suspension of barbituric acid (0.64 g, 5 mmol) and cinnamaldehyde (0.66 g, 5 mmol) in methanol (50 mL) was heated at 80°C for 2 h. The reaction suspension was cooled to room temperature and 4-dimethylaminobenzaldehyde (0.750 g, 5 mmol) and 5% Pt–C (0.5 g) with 67% water was added. The suspension was hydrogenated at 70 psi hydrogen pressure for 4 h at room temperature. The catalyst was separated by filtration, and the filtrate concentrated to a volume of 10 mL and diluted to a volume of 200 mL with water. The resulting white precipitate was separated by filtration and dried at room temperature to give 5-(4-dimethylaminobenzyl)-5-(3-phenylpropyl)barbituric acid (1.55 g, 79%). ^{1}H NMR (DMSO-d_6): δ 7.247 (2H, t, $J=5.7$), (1H, t, $J=5.4$), 7.116 (2H, d, $J=5.7$), 6.775 (2H, d, $J=5.7$), 6.540 (2H, d, $J=5.7$), 2.928 (2H, s, benzyl), 2.797 (6H, s, $N(CH_3)_2$), 2.514 (2H, t, $J=0.018$), 1.912 (2H, m), 1.359 (2H, m); ^{13}C NMR (DMSO-d_6): δ 169.693, 146.289, 146.228, 137.937, 126.550, 125.161, 125.017, 122.719, 118.819, 108.836, 54.040, 40.423, 34.316, 31.570, 23.285. Anal. calcd for $C_{22}H_{25}N_3O_3$: C, 66.64; H, 6.64; N, 11.07. Found: C, 66.32; H, 6.88; N, 10.83.