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Decarbonylation of tetrasubstituted barbituric acids as a versatile method for preparation of *N,N′*,2,2-tetrasubstituted malonamides

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Abstract

A procedure for the preparation of 1,3,5,5-tetrasubstituted-2,3,4(1*H*,3*H*,5*H*)pyrimidinetriones (barbituric acids) through alkylation of the less substituted 2,3,4(1*H*,3*H*,5*H*)pyrimidinetriones (barbituric acids) and decarbonylation of the tetrasubstituted product into the *N,N′*,2,2-tetrasubstituted-manlonamides are described.

Keywords: 2,3,4(1*H*,3*H*,5*H*)pyrimidinetriones (barbituric acids); 1,3,5,5-tetrasubstituted-barbituric acid; *N,N′*,2,2-tetrasubstituted-malonamides; malonamides.

Malonamide derivatives have a broad range of general applications. For instance, quinolyl malonamide derivatives are used in metal complexation.[1] The uptake of metal ions by extraction chromatography was achieved by using dimethyl dibutyl tetradecyl-1,3-malonamide (DMDBT-DMA) as the stationary phase.[2] There is also one special application of malonamide derivatives in pharmaceutical chemistry, which is their control of epileptic seizures.[3] In general, epilepsy refers to any of a variety of disorders marked by disturbed electrical rhythms of the central nervous system, and typically manifests itself in the form of convulsive attacks or seizures. Currently, the prevalence of epilepsy is between 3 and 6 per 1000 of the population.

It was discovered that certain malonamides exhibit anticonvulsant activity. Of all studied malonamide derivatives, the most promising results were obtained for the *N*-benzyl-2,2-disubstituted malonamides, where the 2-alkyl substituents are lower alkyls with 2 to 8 carbon atoms.[3,4] The best method for the preparation of *N*-benzyl-2,2-dialkylmalonamides[5] has been through *C*-alkylation of ethyl cyanoacetate, transformation of the product into *N*-benzyl-2,2-dialkylated-cyanoacetamide by further reaction with benzyl amine, and finally hydrolysis of the cyano group.[6,7] The last reaction is carried out under rather extreme reaction conditions (PPA/H_2SO_4).

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To the best of our knowledge, there are no systematic studies of the biological activity of *N,N′*-disubstituted malonamides as anti-epileptic drugs. One of the reasons is that these compounds are not easily accessible. Here we would like to present a general method for the preparation of these amides by decarbonylation of 2,3,4(1*H*,3*H*,5*H*)pyrimidinetriones (barbituric acids).

Contrary to the decarboxylation reaction, the decarbonylation reaction is not common in organic synthesis.[8] However, there are several practical procedures for decarbonylation of certain acids such as formic, oxalic, triarylacetic, α-hydroxy, and α-keto acids. However, decarbonylation of tetrasubstituted barbituric acids result in almost quantitative yields of malonamides (Table 1).

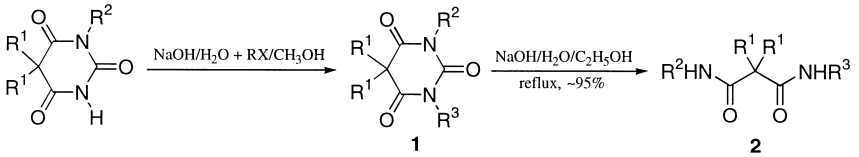

Table 1
Isolated yields for *N*-alkylated-5,5-disubstituted barbituric acids **1** and *N,N′*,2,2-tetrasubstituted malonamides **2**

Substituents	Barbiturate	Yield	Amide	Yield[a]	Yield[b]
R^1=C_2H_5; R^2=$CH_2C_6H_5$; R^3=CH_3	**1a**	94%	**2a**	85%	96%
R^1=C_2H_5; R^2=$CH_2C_6H_5$; R^3=C_2H_5	**1b**	88%	**2b**	85%	96%
R^1=C_2H_5; R^2=$CH_2C_6H_5$; R^3=$(CH_2)_3CH_3$	**1c**	91%	**2c**	85%	96%
R^1=C_2H_5; R^2=$CH_2C_6H_5$; R^3=$(CH_2)_6CH_3$	**1d**	90%	**2d**	85%	96%
R^1=C_2H_5; R^2=R^3=CH_3	**1e**	88%	**2e**	85%	96%
R^1=R^2=C_2H_5	**1f**	85%	**2f**	85%	96%
R^1=C_2H_5; R^2=R^3=$(CH_2)_3CH_3$	**1g**	90%	**2g**	85%	96%
R^1=C_2H_5; R^2=R^3=$(CH_2)_6CH_3$	**1h**	91%	**2h**	85%	96%
R^1=C_2H_5; R^2=R^3=$CH_2C_6H_5$	**1i**	96%	**2i**	85%	97%
R^1=$CH_2C_6H_5$; R^2=R^3=CH_3	**1j**	97%	**2j**	85%	96%
R^1=$CH_2C_6H_5$; R^2=R^3=C_2H_5	**1k**	98%	**2k**	85%	96%
R^1=$CH_2C_6H_5$; R^2=R^3=$(CH_2)_3CH_3$	**1l**	96%	**2l**	85%	96%
R^1=$CH_2C_6H_5$; R^2=R^3=$(CH_2)_6CH_3$	**1m**	90%	**2m**	85%	96%
R^1=R^2=R^3=$CH_2C_6H_5$	**1n**	98%	**2n**	85%	96%

[a]Decarbonylation of the barbituric acid; [b]alkylation-followed by decarbonylation of the barbituric acid

Many of the barbituric acid derivatives are commercially available or they can be readily prepared from diethyl malonates and urea.[9] On the other hand, 1,3,5,5-tetrasubstituted barbituric acid can be prepared in almost quantitative yield by alkylation of the 5,5-disubstituted barbituric acid.[10] Unfortunately, preparation of 1,3-asymmetric tetrasubstituted barbituric acid by double *N*-alkylation usually produces a mixture of all three products, which are hard to separate. But if preparation starts with pure mono *N*-alkylated barbituric acid, introducing a second *N′*-alkyl group and isolation of product is almost quantitative. In both cases the reaction of alkylation consisted of simple mixing of equivalent amounts of barbituric acid, sodium hydroxide, and the alkylating reagent in water/ethanol.[10] The reaction mixture was stirred at room temperature for several hours, and refluxed for several additional hours. The isolation of the product comprises of

the evaporation of the alcohol, extraction with chloroform, and recrystallization. It is also important to notice that the amount of the base in process of alkylation is very important. If a substantial excess (~50%) of the base (NaOH) is used, a considerable amount of decarbonylation product is isolated as a byproduct. About 10% excess of the base seems to produce the best alkylation results.

Decarbonylation of the tetrasubstituted barbituric acids is also a very simple procedure.[11] A mixture of tetrasubstituted barbituric acid and 2.2 equivalents of sodium hydroxide in ethanol/water was refluxed for several hours. After the evaporation of ethanol, *N*,*N*′-disubstituted malonamides **2** were isolated by chloroform extraction or recrystallized to a white solid insoluble in water. It is not necessary to perform *N*-alkylation of barbituric acid and then decarbonylation of the alkylated product separately. These reactions can be carried out as a one-pot synthesis.[12] In this case, the isolated yields of the malonamides are even higher (Table 1) and purity of the isolated malonamides comparable (more than 98%) to their two-step synthesis.

Unfortunately, the decarbonylation procedure is not helpful for the preparation of amides if one of the NH groups of the barbituric acid is free. The hydroxide ion is a stronger base than it is nucleophile for the ring opening, therefore a salt of barbituric acid is formed. Once formed, decarbonylation of the salt does not occur. In fact, the monoalkylated 1-benzyl-5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione was separated from the dialkylated 1,3-dibenzyl-5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione by transformation of the latter into the easily separable *N*,*N*′-dibenzyl-2,2-diethylmalonamide.

References

1. Hiratani, K. US Patent No. 5,071,989, 1991.
2. Mohapatra, P. K.; Sriram, S.; Badheka, L. P. *Sep. Sci. Technol.* **2000**, *35*, 39; Chan, Gabriel, Y. S.; Drew, M. G. B.; Madic, C. *J. Chem. Soc., Dalton Trans.* **1997**, 647; Iveson, P. B.; Drew, M. G. B.; Madic, C. *J. Chem. Soc., Dalton Trans.* **1999**, 3605; Hiratani, K.; Taguchi, K.; Ohashi, K. *Chem. Lett.* **1989**, 2073.
3. Darling, C. N. US Patent No. 4,537,781, 1985.
4. *The Profile of Anticonvulsant Activity and Acute Toxicity of 56098 and Some Prototype Antiepileptic Drugs in Mice and Rates*, with reported dated 7/2/82 and number 38. Results are taken from Ref 1.
5. Draling et al. In *J. Pharm. Sci.* **1979**, *69*, 108.
6. Dermer, O. C.; King, J. *J. Org. Chem.* **1943**, *8*, 168.
7. Patel et al. *Journal Sci. Industr. Res.* **1961**, *20B*, 457.
8. March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; pp. 732–733.
9. For instance, see: *Vogel's Text-Book of Synthetic Organic Chemistry*, 3rd ed.; New York, 1966; pp. 1001–1005.
10. **A general method for preparation of tetrasubstituted barbituric acids**. Preparation of 5,5-dibenzyl-1,3-dimethyl-2,3,4(1*H*,3*H*,5*H*)pyrimidinetrione (**1j**): The 5,5-dibenzyl-2,3,4(1*H*,3*H*,5*H*)pyrimidinetrione (3.08 g, 0.01 mol) was dissolved in an aqueous (50 mL) sodium hydroxide (0.88 g, 0.022 mol) and ethanol (50 ml). The solution of dimethyl sulfate (2.52 g, 0.02 mol) was added. Temperature of the reaction mixture shortly afterwards increased and the reaction mixture became a suspension. Stirring of the reaction mixture was continued while refluxing for 3 hours. Ethanol was evaporated and the remaining white suspension was extracted with chloroform (3×150 ml). Combined chloroform extracts were washed with aqueous sodium hydroxide (20% sodium hydroxide, 3×50 ml), dried and evaporated. The solid residue was slurred in cold petroleum ether and separated by filtration. The yield of the reaction was 97%; m.p. ~225°C with decomposition. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, t), 7.19 (4H, dd); 7.07(4H, t) 3.45(6H, s), and 2.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.6 (C-4,C-6), 149.8 (C-2), 134.9, 129.1, 128.4, 127.5 (aromatics), 61.0 (C-5), 45.1 (CH_2), and 27.9 (CH_3) ppm; MS (CI) *m*/*z* 336 (M^+), 308 (M^+–CO), 281(M^+–$CONCH_2$), 245(M^+–$C_6H_5CH_2$), 217 ($C_6H_5C{=}C(CONHCH_3)_2^+$), 188 ($C_6H_5CH{=}C(CO)CONHCH_3^+$), 1 9 ($C_6H_5CH{=}CH{-}CON{=}CH_2^+$), 131 ($C_6H_5CH{=}CHCO^+$), 103 ($C_6H_5CH{=}CH^+$), 91($C_6H_5CH_2^+$); anal. calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.33; H, 6.03; N, 8.27.

11. **A general procedure for decarbonylation of barbituric acids**. Preparation of *N,N′*-dibenzyl-2,2-diethylmalonamide (**2i**). 5,5-Dienthyl-1,3-diphenylmethyl-2,3,4(1*H*,3*H*,5*H*)-pyrimidinetrione (3.64 g, 0.01 mol) solution in 95% ethanol (100 mL) was dissolved in aqueous (100 mL) sodium hydroxide (0.8 g, 0.02 mol) and refluxed overnight. Ethanol was evaporated and the white solid residue was separated by filtration. White crystals were washed with water (3×50 mL) and recrystallized from 95% ethanol. The yield of the product was 3.38 g (97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (2H, t, $J_2=0.019$, NH), 7.29 (10H, m, C_6H_5); 4.44 (4H, d, $J_2=0.019$, 1.91 (4H, q, $J_2=0.024$, CH_2CH_3), 0.84 (6H, t, $J_2=0.024$, CH_2CH_3) 1.81 (4H, q, $J_2=0.025$, CH_2CH_3) and 0.74 (6H, t, $J_2=0.025$, CH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 172.9 (C-1), 138.1, 128.4, 127.4 and 127.1 (aromatics), 58.0 (C-2), 43.4 (CH_2-benzyl), 30.1 (CH_2-ethyl), and 9.3 (CH_3–ethyl) ppm; MS *m*/*z* 339 ($M+1^+$); 338 (M^+), 232 (M^+–$NHCH_2Ph$); anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.41; H, 7.85; N, 8.15.
12. **A general procedure for direct preparation of malonamides from 5,5-disubstituted barbituric acid**. Preparation, *N,N′*-dimethyl-2,2-diethylmalonamide (**2e**): Sodium 5,5-diethylbarbiturate (2.06 g, 0.01 mol) was dissolved in aqueous (20 mL) sodium hydroxide (0.44 g, 0.011 mol). Into this solution, ethanolic (50 ml) solution of dimethyl sulfate (2.52 g, 0.02 mol) was added. The clear reaction mixture was stirred at room temperature for 0.5 hour and the solvent was evaporated. The oily residue was dissolved in 60% ethanol (100 mL), and sodium hydroxide (1.76 g, 0.044 mol) was added. The reaction mixture was refluxed for 1 hour. Ethanol was evaporated. White crystals in water residue was extracted with chloroform (3×50 mL). Combined chloroform layers were dried and evaporated to dryness. The remaining white crystals were slurred in cold petroleum ether and filtered affording 1.8 g (97%) of the product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, t, $J_2=0.016$, NH), 2.76 (6H, d, $J_2=0.016$, NCH_3), 1.81 (4H, q, $J_2=0.025$, CH_2CH_3) and 0.74 (6H, t, $J_2=0.025$, CH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 173.8 (C-1), 57.9 (C-2), 26.2 (CH_2), and 9.3 (CH_3) ppm; MS (CI) *m*/*z* 187 ($M+1^+$), 186 (M^+), 171 (M^+–CH_3), 158 ($M+1^+$–C_2H_5), 143 ($M+1^+$–CH_3NHCH_3), 129 (M^+-$OCNCH_3$), 100 ($CH_3CH_2CHCONHCH_3^+$); anal. calcd for $C_9H_{18}N_2O_2$: C, 58.04; H, 9.74; N, 15.04. Found: C, 57.96; H, 9.83; N, 14.96.