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Three-Component, One-Pot Sequential Synthesis of *N*-Aryl, *N*′-Alkyl Barbiturates§

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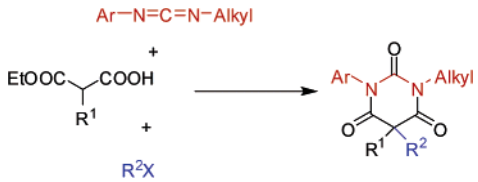
ABSTRACT



Condensation between *N*-alkyl, *N*′-aryl carbodiimides and malonic acid monoesters leads to a high-yield formation of *N*-acyl urea derivatives that could be cyclized to C-monosubstituted barbiturates by addition of a suitable base in a one-pot sequential fashion. In the presence of an electrophile, the last step gives rise to a one-pot, three-component sequential synthesis of fully substituted barbiturates.

The main emphasis of the pharmaceutical industry's improved performance in the reaction synthesis of targets was the demonstration of considerable waste reduction by reducing the number of isolations of intermediates along a given pathway by concatenating one reaction into the next.[1] Efficiency is also being currently pursued, when possible, by implementation of classical multicomponent reactions (MCRs) as well as by the invention of new ones.[2] In this context, one-pot MC sequential synthesis features a high degree of reaction mass efficiency[3] and is especially suited for applications in combinatorial chemistry and diversity-oriented synthesis.

Barbiturates are a well-known class of compounds with various pharmacological activities[4] and have been widely used in the manufacturing of plastics,[5] textiles,[6] and polymers[7] and as useful building blocks in assembling supramolecular structures via noncovalent interactions.[8] The fact that barbituric acid derivatives have been employed in medicinal practice for a long time by no means implies that all of the problems related to their synthesis are solved. The general route for their preparation is through the condensation of urea and malonic ester derivatives with sodium alcolate in dry ethanol or DMSO at high temperature.[9] However, the yields of this reaction are often low due to the presence of side reactions such as hydrolysis of the malonate, decar-

§ This communication is dedicated to Prof. Pierfrancesco Bravo on the occasion of his retirement.

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‡ C.N.R. Istituto di Chimica del Riconoscimento Molecolare.

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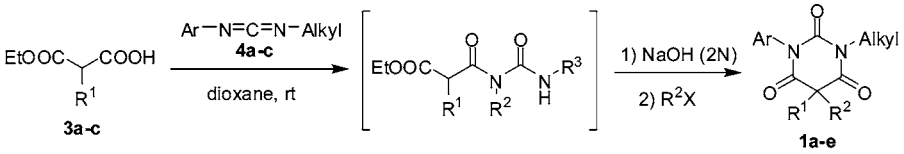
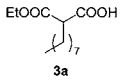
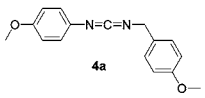
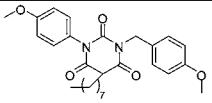
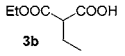
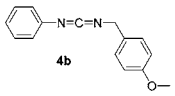
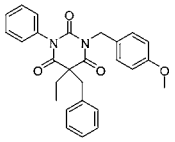
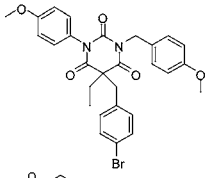
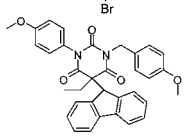
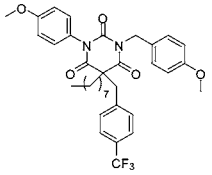
Table 1. Three-Component Sequential Synthesis of Barbiturates **1a**,**e** Using the NaOH\Dioxane Protocol



entry	malonic acid monoester	carbodiimide	alkyl halides	barbituric acid	product, yield (%)
1			None		**1a**, 83
2					**1b**, 67
3	**3b**	**4a**			**1c**, 62
4	**3b**	**4a**			**1d**, 65
5	**3a**	**4a**			**1e**, 60

boxylation, transesterification, and urea degradation.[10] With this in mind, we aimed at developing a new synthesis of barbiturates that was practical, experimentally simple, and efficient for the one-pot generation of several new chemical bonds.

Recently, we demonstrated that the reaction of activated α,β-unsaturated carboxylic acids with carbodiimides that occurs through a novel one-pot multistep reaction represents a viable entry to hydantoines.[11] Now we show that the reaction of *N*-alkyl, *N*′-aryl carbodiimides **4** (Figure 1) with malonic acid monoesters **3** in the presence of alkyl halides that takes place through a three-component, one-pot sequential process involving *N*-acyl ureas **2** as intermediates affords a wide array of structurally diverse barbiturates **1**.

The starting malonic acid monoesters **3a**−**c** were prepared either by alkylation of the commercially available benzyl ethylmalonate **5** promoted by NaH in DMF followed by hydro-debenzylation or by carboxylation of the corresponding metalated ethyl ester **6** with CO_2 (Scheme 1).

Carbodiimides[12] when reacted with carboxylic acids rapidly form *O*-acyl isourea intermediates that in the absence

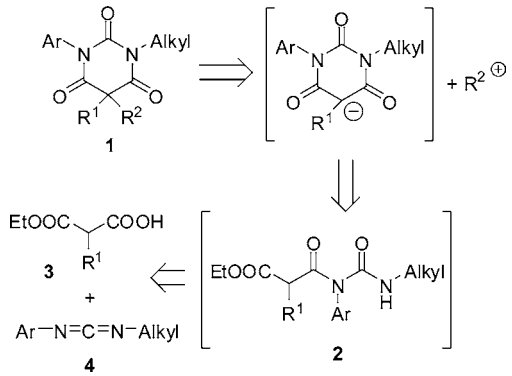


Figure 1. Retrosynthetic analysis.

of a nucleophile undergo a rearrangement, the so-called O → N acyl migration, to give *N*-acyl ureas.[13] Because it was known that treatment of *N*-acyl ureas of type **2** with aqueous NaOH in dioxane promotes ring closure affording barbiturates in good yields,[14] we decided to use these conditions to perform our MC reaction in a sequential fashion. Accord-

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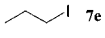
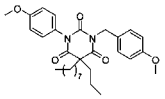
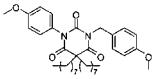
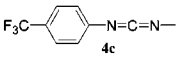
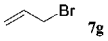
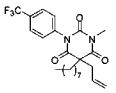
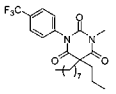
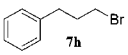
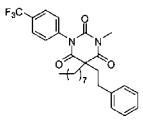
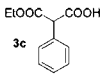
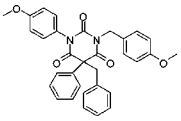
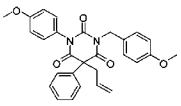
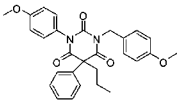
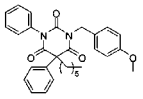
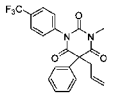
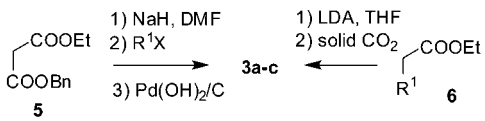
Table 2. Three-Component Sequential Synthesis of Barbiturates **1f,o** Using the K_2CO_3\CH_3CN Protocol

entry	malonic acid mono-ester	carbodiimide	alkyl halides	barbituric acid	product, yield (%)
1	**3a**	**4a**	 **7e**		**1f** ,80
2	**3a**	**4a**	 **7f**		**1g**, 73
3	**3a**	 **4c**	 **7g**		**1h**, 90
4	**3a**	**4c**	**7e**		**1i**, 65
5	**3a**	**4c**	 **7h**		**1j**, 61
6	 **3c**	**4a**	**7a**		**1k**, 71
7	**3c**	**4a**	**7g**		**1l**, 70
8	**3c**	**4a**	**7e**		**1m**, 52
9	**3c**	**4b**	 **7i**		**1n**, 55
10	**3c**	**4c**	**7g**		**1o**, 67
11	**3c**	**4c**	**7h**	/	No reaction obsd.

ingly, the condensation between carboxylic acid **3a** (Table 1, entry 1) and carbodiimide **4a** in dioxane (rt, overnight) followed by one-pot addition of a 2 N NaOH aqueous solution gave the barbituric acid **1a** in a few minutes and in very good yields.

Scheme 1. Synthesis of the Starting Malonic Acid Monoesters **3**



3a $R^1 = n\text{-}C_8H_{17}$ (89%); **3b** $R^1 = n\text{-}C_2H_5$ (87%); **3c** R^1 = Ph (98%)

Unfortunately, the addition of the electrophile after the cyclization step gave satisfactory yields only with highly reactive benzyl bromides (Table 1, entries 2−5). Other halides, such as alkyl and even allyl halides, gave very poor yields or did not react at all.[15] Moreover, only barbiturates that were N-aromatic "neutral" (Table 1, entry 2) or electron rich (Table 1, entries 3−5) gave the desired products, whereas electron-poor *N*-aryl barbiturates and *C*-aryl-

substituted malonic acid monoester **3c** did not react with any benzyl halide affording only monosubstituted barbiturates.

Surprisingly, in the literature, we could not find any simple general procedure for the C-alkylation of barbituric acids. Thus, after screening several combinations of solvents and bases for sequential cyclization and alkylation of *N*-acyl ureas **2**, we were able to find a suitable procedure consisting of the use of a suspension of anhydrous K_2CO_3 in acetonitrile in a sealed tube at 120 °C (Table 2). 2-Octyl malonic acid monoesters **3a** underwent a three-component reaction with electron-rich carbodiimide **4a** and *n*-propyl iodide **7e** (Table 2, entry 1) or *n*-octyl bromide **7f** (Table 2, entry 2) producing C-disubstituted barbiturates **1f** and **1g**, respectively, in very good yields.

Even when **3a** was reacted with the electron-poor carbodiimide **4c**, the final products **1h**−**j** were obtained in excellent to good yields depending on the reactivity of the alkyl halide used in the third step of the sequential pathway (Table 2, entries 3−5, respectively). 2-Phenylmalonic acid monoethyl ester **3c** reacted with electron-rich carbodiimide **4a** giving rise to the formation of C-disubstituted barbiturates **1k**,**l** in very good yield with highly reactive benzyl bromide **7a** and allyl bromide **7g**, respectively (Table 2, entries 6 and 7), whereas with the less reactive *n*-propyl iodide **7e**, the final product **1m** was obtained in acceptable yield (Table 2, entry 8). **3c** reacted also with phenyl-substituted carbodiimide **4b** in the presence of *n*-hexyl iodide **7i** giving rise to the formation of barbiturate **1n** in acceptable yield (Table 2, entry 9). Finally, alkylation of the barbiturate obtained by condensation of electron-poor carbodiimide **4c** with **3c** occurred only with highly reactive alkyl halides such as allyl bromide **7g** (Table 2, entry 10), whereas no reaction was detected with less reactive 3-phenylethyl bromide **7h** (Table 2, entry 11).

In conclusion, we have developed a novel and efficient process for the synthesis of a wide range of structurally diverse *N*-alkyl, *N*′-aryl barbiturates by a three-component sequential reaction involving malonic acid monoesters, carbodiimides, and alkyl halides. This process generates compounds with a high level of diversity from simple and readily accessible starting materials. Furthermore, the operational simplicity and good chemical yield, combined with favorable atom-economy aspects and a small number of steps, make this new synthetic strategy highly attractive and promising for the preparation of barbiturate compounds with potential synthetic and biological uses.

Acknowledgment. Politecnico di Milano and CNR are gratefully acknowledged for economic support.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a review on carbodiimide chemistry, see: Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589−636. For a pioneering work on the synthesis of barbituric acids from malonic acids and carbodiimides, see: Bose, K. A.; Garratt, S.; Pelosi, J. J. *J. Org. Chem.* **1963**, *28*, 730−733.

(13) (a) Rebek, J.; Fitler, D. *J. Am. Chem. Soc.* **1973**, *95*, 4052−4053. (b) Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1974**, *96*, 1606−1607. (c) Rebek, J.; Feitler, D *Int. J. Pept. Protein Res.* **1975**, *7*, 167.

(14) Graziano, M. L.; Cimminiello, G. *Synthesis* **1989**, *1*, 54−56.

(15) Increasing the temperature during the last step resulted in the formation of complex mixtures.