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Multicomponent, One-Pot Sequential Synthesis of 1,3,5- and 1,3,5,5-Substituted Barbiturates†

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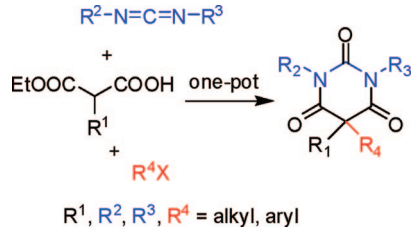

Carbodiimides and malonic acid monoethylesters readily react to afford *N*-acylurea derivatives that could be cyclized in situ by addition of a suitable base. This process represents a general and straightforward one-pot sequential synthesis of 1,3,5-trisubstituted barbiturates in very mild conditions (organic solvent/2 N NaOH aqueous solution, 20 °C). Performing the reaction in the presence of an electrophile resulted in the formation of fully substituted (namely, 1,3,5,5-tetrasubstituted) barbiturates through a three-component one-pot sequential process. The latter, however, occurred only with highly reactive electrophiles, such as benzyl and, in some instances, allyl halides. In order to expand the scope of the process, we sought to develop a general method for the C-alkylation of 1,3,5-trisubstituted barbiturates. We found that C-alkylation occurred upon treatment of 1,3,5-trisubstituted barbiturates with an alkyl halide in CH_3CN at 120 °C in the presence of anhydrous K_2CO_3 affording the target 1,3,5,5-tetrasubstituted barbiturates in good yields. The multicomponent process was accomplished by combining the three steps in a one-pot sequential fashion, i.e., the condensation of carbodiimides with malonic acid monoethylesters, the cyclization of the resulting *N*-acylureas, and the C-alkylation of the resulting 1,3,5-substituted barbiturates. A detailed study of the influence of the structure of the reactants on the reaction outcome and mechanism is presented. By selective *N*′-deprotection of 1,3,5,5-tetrasubstituted barbiturates, the corresponding 1,5,5-trisubstituted barbiturates were also prepared.

Introduction

Although the past 50 years have witnessed extraordinary progress in the discovery of new reagents, reactions, and synthetic strategies,[1] the tools of synthetic organic chemistry are often found inadequate when confronted with the challenge of preparing even modestly elaborate molecules in practical fashion. One powerful approach toward this goal is to combine two or more distinct reactions into a single transformation, thereby producing a sequential reaction process. One-pot processes involving sequential steps are subdivided into two main families, i.e., domino reactions and consecutive reactions, independently of the reaction mechanism.[2] In domino (often referred to as tandem or cascade) reactions, reagents and catalysts are mixed together and experimental conditions are

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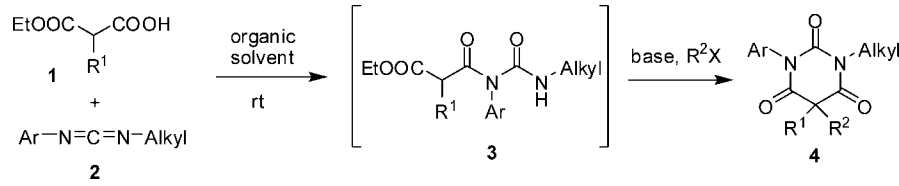

FIGURE 1. Three-component one-pot synthesis of *N*-alkyl,*N*′-aryl barbiturates.

set up in such a way to promote the reaction cascade: each bond-forming step results as a consequence of the functionality left by the previous reaction. In consecutive reactions the first step does not promote the second one and external reagents or changes in reaction conditions are required to favor propagation. Both processes allow the efficient construction of complex molecules from simple precursors in a minimum number of steps and are ideally suited for the generation of structurally diverse libraries of small molecules. One-pot processes involving sequential steps are further divided into unicomponent, in which a single starting molecule undergoes a sequence of intramolecular processes, and multicomponent (MC) processes.[3] Efficiency is also being pursued, when possible, by implementation of classical MC reactions, as well as by the invention of new ones. In this context "one-pot" MC sequential syntheses in which a number (≥2) of synthetic steps involving two or more reactants are carried out in the same flask without isolation of any intermediate feature a high degree of reaction mass efficiency[4] and are especially suitable in combinatorial chemistry and diversity-oriented synthesis programs.

Many small synthetic organic molecules with high medicinal potential contain heterocyclic rings. The range of easily accessible and suitably functionalized heterocyclic building blocks is, however, surprisingly limited, and the construction of even a small array of relevant heterocyclic compounds is far from trivial. Heterocyclic chemistry therefore continues to attract the attention of medicinal and synthetic chemists,[5] and the development of novel methodologies allowing for efficient access to heterocycles is still highly beneficial. Traditionally, methods based on MC reactions have proved quite efficient for the construction of many different types of heterocycles.[6] Barbiturates are a popular class of heterocycles with a number of pharmacological activities[7] and have been widely used also in the manufacturing of plastics,[8] textiles,[9] polymers[10] and as useful building blocks in assembling supramolecular structures via noncovalent interactions.[11] In medicinal chemistry, further to their very well-established use as hypnotics, derivatives of barbituric acid have been reported to exhibit anticancer, analeptic, immunomodulating, and anti-AIDS activity, while others are reported to be selective matrix metalloproteinase (MMP) inhibitors.[12] The fact that barbituric acid derivatives have been employed in medicinal practice for a long time by no means implies that all or at least some of the problems related to their synthesis are solved. The use of combinatorial approaches to the synthesis of the barbiturate scaffold would be a powerful advance in helping to speed up drug discovery. The general route for the synthesis of barbiturates is the condensation of urea and malonic ester derivatives with sodium alcolate in ethanol or DMSO.[13] The yields of this reaction are often modest due to the presence of side reactions such as hydrolysis of the malonate, decarbethoxylation, transesterification, and urea degradation. Moreover, the need for dry solvents and high temperature and the use of inert atmosphere and metallic sodium hamper the use of the classical synthesis of barbiturates for combinatorial purposes and diversity-oriented synthesis programs. Another way to prepare barbiturates could be the alkylation of unsubstitued barbituric acid. However, to the best of our knowledge, there was no simple general synthetic procedure for the preparation of 5-monoalkylated barbiturates until quite recently, when Juric et al. described an effective reductive alkylation protocol in the presence of platinum and palladium catalysts.[14] With this in mind, we envisioned developing a new synthesis of barbiturates that was practical yet experimentally simple, chemically efficient by generating multiple bonds in one pot, and tolerant of multiple functional groups, allowing for the preparation of *N*-mono- and *N*,*N*′-disubstituted 5-mono- and 5,5-disubstituted barbiturates.

Very recently, we reported a new three-component, one-pot sequential process for the synthesis of a large array of fully substituted structurally diverse *N*-alkyl,*N*′-aryl barbiturates.[15] By reacting *N*-alkyl,*N*′-aryl carbodiimides **2** with malonic acid monoesters **1** we obtained the formation of *N*-acyl urea derivatives **3** that underwent one-pot cyclization and alkylation in the presence of a base and an alkylating agent affording the desired *N*-alkyl,*N*′-aryl 5,5-disubstituted barbiturates **4** in high yields (Figure 1).

In this paper, we provide a full account on the scope and limits of this methodology, which has been studied in detail by performing the reaction with other carbodiimides, namely, *N*,*N*′-dialkyl and *N*,*N*′-diaryl carbodiimides. Moreover, we disclose herein a practical procedure for the C-alkylation of barbituric acids that, surprisingly, was missing in the literature. The new results remarkably expand the scope of the process, allowing

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CHART 1. Synthesis of Starting Malonic Acid Monoethylesteres 1

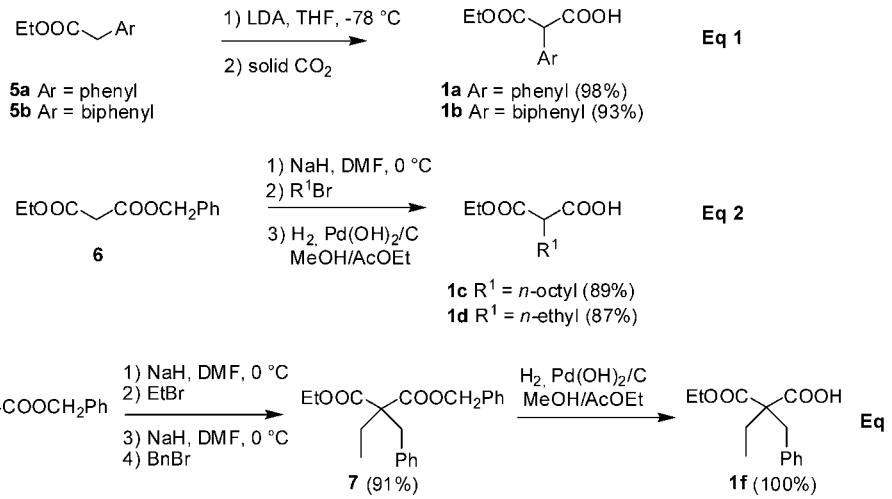
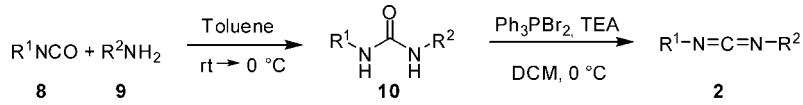


CHART 2. Synthesis of Carbodiimides 2



***N*-alkyl, *N'*-aryl carbodiimides**
2a R^1 = Ph, R^2 = *c*-hexyl (72%)
2b R^1 = Ph, R^2 = 4-MeO-Ph-CH_2 (75%)
2c R^1 = 4-MeO-Ph, R^2 = 4-MeO-Ph-CH_2 (74%)
2d R^1 = Ph, R^2 = $PhCH_2$ (77%)
2e R^1 = 4-CF_3-Ph, R^2 = Me (64%)

***N*,*N'*-diaryl carbodiimides**
2f R^1 = R^2 = *p*-Tol (commercial)
2g R^1 = R^2 = 4-MeO-Ph (86%)
2h R^1 = 4-NO_2-Ph, R^2 = 4-MeO-Ph (88%)

***N*,*N'*-dialkyl carbodiimides**
2i R^1 = R^2 = *iso*-propyl (commercial)
2j R^1 = 4-MeO-Ph-CH_2, R^2 = Trityl (62%)
2k R^1 = Ph-CH_2, R^2 = Trityl (65%)

for the preparation of a large array of structurally diverse 1,3,5- and 1,3,5,5-substituted barbiturates.

Results

Synthesis of Starting Materials. The starting *C*-aryl malonic acid monoesters **1a,b** were obtained in almost quantitative yields directly by carboxylation of the corresponding metalated ethyl esters **5a,b** with solid CO_2 (Chart 1, eq 1). While malonic acid monoethylester $HO_2CCH_2CO_2Et$ (**1e**) is commercially available, *C*-monoalkyl derivatives **1c,d** were prepared by alkylation of the commercially available benzyl ethylmalonate **6** promoted by NaH in dry DMF followed by *O*-debenzylation (Chart 1, eq 2). Finally, *C*-dialkyl malonic acid monoster **1f** was prepared by sequential alkylations of **6** followed by *O*-debenzylation (Chart 1, eq 3).

Carbodiimides **2**,[16] when not commercially available like bis-*p*-tolyl carbodiimide (**2f**) and DIC (**2i**), were all prepared in good yields by dehydration with freshly prepared bromotriphenylphosphorane of the corresponding ureas **10**,[17] which were prepared by reaction of isocyanates **8** with amines **9** in toluene and purified by short-path flash chromatography (Chart 2).

Synthesis of 1,3,5-Substitued Barbiturates. Carbodiimides are very popular reagents often used to activate carboxylic acid groups to nucleophilic substitutions and coupling reactions.[18] The mechanism and kinetics of the reaction of carbodiimides with carboxylic acids have been extensively investigated.[19] Recently carbodiimides have been also used for the synthesis of small heterocycles containing the key *N*-acylurea moiety.[20] In this context, we undertook a study on the synthesis of barbiturates **11**, a class of "*N*-acylurea-heterocycles", through reaction of monoesters **1** with carbodiimides **2**, followed by one-pot cyclization of the resulting *N*-acylurea **3** promoted by in situ addition of a suitable base. Since treatment of *N*-acylureas **3** with aqueous NaOH in dioxane is known to promote ring closure affording barbiturates in good yields,[21] we decided to study the process using dioxane and other solvents that can be mixed with water, in order to perform the process in a "one-pot" sequential fashion. Accordingly, malonate **1a** reacted with carbodiimides **2a,f** in THF (entries 1 and 11, Table 1), dioxane (entries 2 and 12), and acetonitrile (entries 3 and 13) affording *N*-acylureas **3a** and **3j** as the only regioisomers, in good yields. The best results were obtained in dioxane, and thus we selected this solvent to perform the reaction in sequential manner. First, we investigated the reaction of malonates **1** with *N*-alkyl,*N'*-aryl carbodiimides **2a**−**e**.

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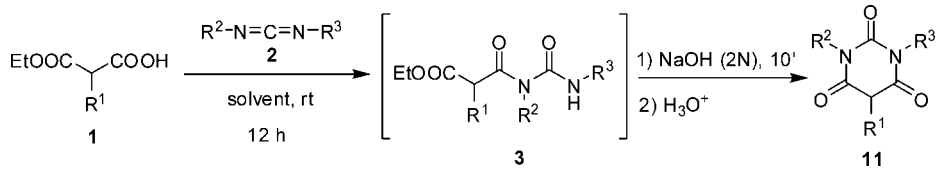
TABLE 1. One-Pot Sequential Synthesis of Barbituric Acids 11



entry	malonic acid	R^1	carbodiimide	R^2	R^3	solvent	product	yield (%)
1	**1a**	Ph	**2a**	Ph	*c*-hexyl	THF	**3a**	70[a]
2	**1a**	Ph	**2a**	Ph	*c*-hexyl	dioxane	**3a**	75[a]
3	**1a**	Ph	**2a**	Ph	*c*-hexyl	CH_3CN	**3a**	73[a]
4	**1a**	Ph	**2a**	Ph	*c*-hexyl	dioxane	**11a**	68
5	**1a**	Ph	**2b**	Ph	PMB	dioxane	**11b**	73
6	**1a**	Ph	**2c**	PMP	PMB	dioxane	**11c**	85
7	**1b**	4-diphenyl	**2b**	Ph	PMB	dioxane	**11d**	76
8	**1c**	*n*-octyl	**2a**	Ph	*c*-hexyl	dioxane	**11e**	75
9	**1c**	*n*-octyl	**2c**	PMP	PMB	dioxane	**11f**	83
10	**1c**	*n*-octyl	**2b**	Ph	PMB	dioxane	**11g**	75
11	**1c**	*n*-octyl	**2e**	*p*-CF_3-Ph	Me	dioxane	**11h**	80
12	**1a**	Ph	**2f**	*p*-Tol	*p*-Tol	THF	**3j**	65[a]
13	**1a**	Ph	**2f**	*p*-Tol	*p*-Tol	dioxane	**3j**	75[a]
14	**1a**	Ph	**2f**	*p*-Tol	*p*-Tol	CH_3CN	**3j**	70[a]
15	**1a**	Ph	**2f**	*p*-Tol	*p*-Tol	dioxane	**11j**	75
16	**1a**	Ph	**2f**	*p*-Tol	*p*-Tol	CH_3CN	**11j**	50
17	**1a**	Ph	**2g**	PMP	PMP	dioxane	**11k**	82
18	**1c**	*n*-octyl	**2f**	*p*-Tol	*p*-Tol	dioxane	**11l**	77
19	**1c**	*n*-octyl	**2g**	PMP	PMP	dioxane	**11m**	71
20	**1c**	*n*-octyl	**2h**	4-NO_2-Ph	PMP	dioxane	**11n**	79
21	**1d**	ethyl	**2f**	*p*-Tol	*p*-Tol	dioxane	**11o**	74
22	**1a**	Ph	**2i**	*i*-Pr	*i*-Pr	dioxane	**3p**	0[a,b]
23	**1a**	Ph	**2i**	*i*-Pr	*i*-Pr	CH_3CN	**3p**	0[a,b]
24	**1a**	Ph	**2i**	*i*-Pr	*i*-Pr	DCM	**3p**	67[a,d]
25	**1a**	Ph	**2i**	*i*-Pr	*i*-Pr	DCM	**11p**	67[a,d,e]
26	**1d**	ethyl	**2i**	*i*-Pr	*i*-Pr	dioxane	**3q**	n.d.[a,c]
27	**1c**	*n*-octyl	**2i**	*i*-Pr	*i*-Pr	DCM	**3r**	68[a,d]
28	**1a**	Ph	**2j**	PMB	trityl	dioxane	**3s**	71[a]
29	**1a**	Ph	**2j**	PMB	trityl	dioxane	**11s**	68
30	**1a**	Ph	**2k**	Bn	trityl	dioxane	**11t**	67
31	**1d**	ethyl	**2k**	Bn	trityl	dioxane	**3u**	65[a]
32	**1d**	ethyl	**2k**	Bn	trityl	dioxane	**11u**	62

[a] Reactions stopped after formation of intermediates **3**. [b] Only dercarboxylation occurred. [c] Not determined because decarboxylation occurred in much higher yields. [d] Performed with 1 equiv of TMP. [e] The cyclization step was complete in 12 h.

Both *C*-aryl malonates **1a,b** (entries 4−7, Table 1) and *C*-monoalkyl malonate **1c** (entries 8−11, Table 1) gave barbiturates **11a**−**h** in good yields upon overnight reaction at room temperature with the *N*-alkyl,*N*′-aryl carbodiimides **2a**−**e**, followed by in situ addition of a 2 N aqueous solution of NaOH. This process represents a general entry to 1,3,5-substituted barbiturates **11** because it worked well in all cases, namely, when the aryl group R^2 of the carbodiimide was "neutral" (entries 5, 7, 8, 10), electron-rich (entries 6, 9), or electron-poor (entry 11). Next, we investigated the behavior of *N*,*N*′-diaryl carbodiimides **2f**−**h**. As expected, barbituric acid **11j** was formed in good yield when the two-step process was performed in dioxane (entry 15), whereas in acetonitrile we obtained the formation of **11j** in only moderate yield (entry 16), confirming that dioxane is the best solvent for this reaction. It is worth noting that the reaction worked well in all cases, namely, with *C*-aryl malonates **1a** (entries 15 and 17) and *C*-monoalkyl malonates **1c,d** (entries 18−21) and with symmetric (entries 15−19 and 21) and asymmetric (entry 20) carbodiimides.

Unexpectedly, dialkylcarbodiimides such as DIC **2i** produced only decarboxylation of the starting malonate **1a** (entries 22 and 23). Only with 2-ethyl malonate **1d**, which is less acidic than **1a**, we observed the formation of the target *N*-acylurea **3q**, albeit in very low yields since decarboxylation was still the major outcome (entry 26). Moreover, it was shown that carboxylic acids possessing a strong electron-withdrawing group in the α-position, such as malonic acids, undergo facile dehydration upon reaction with carbodiimides to form the corresponding highly reactive substituted ketenes.[22] In order to overcome these problems, we though to perform the reaction using a less polar solvent, such as DCM, and in the presence of a base, namely, *sym*-collidine (TMP), which should facilitate the O→N acyl migration process leading to the formation of the *N*-acylurea derivatives **3**. Gratifyingly, using these conditions we were able to suppress almost completely the above-mentioned side reactions, obtaining *N*-acylureas **3p** and **3r** as the major products in good yields (entries 24 and 27), respectively from *C*-aryl and *C*-alkyl malonates **1a** and **1c**. Moreover, we found that in situ addition of a 2 N aqueous NaOH solution promoted the cyclization step under Schotten−Baumann condition leading to the formation of barbiturates **11p** in good yield (entry 25, Table 1).[23] Dialkylcarbodiimides bearing an electron-withdrawing *N*-trityl substituent, such as **2j**,**k**, reacted smoothly in dioxane both with *C*-aryl malonate **1a** (entry 28) and *C*-monoalkyl malonate **1d** (entry 31) leading to the

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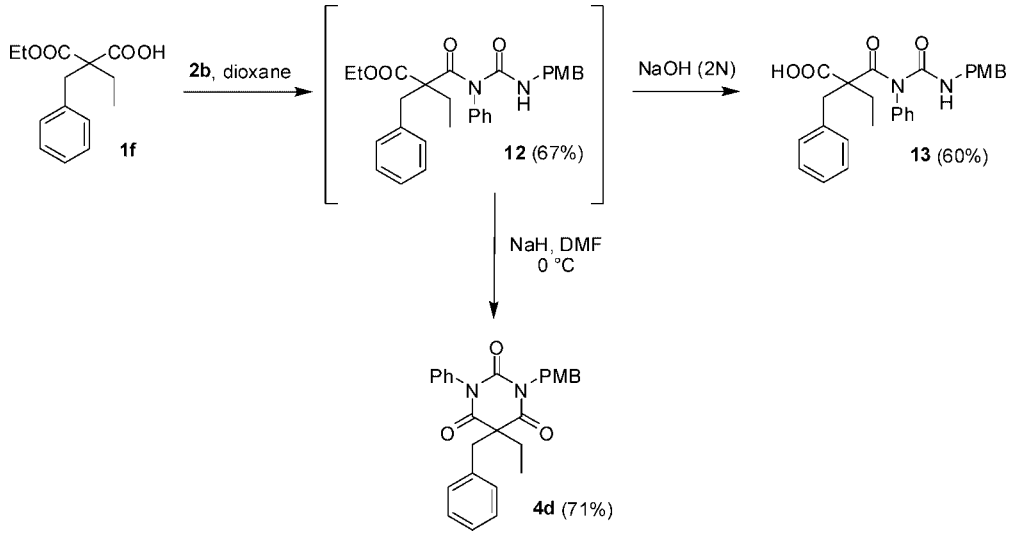
SCHEME 1. Reaction with C-Disubstituted Malonic Acid Monoethylester 1f



formation of *N*-acylureas **3s** and **3u**, respectively, in good yields. As expected, cyclization occurred in almost quantitative yields (data not shown) giving rise to the formation of barbiturates **11s**,**t**,**u** (entries 29, 30, 32) under the sequential reaction conditions. Disappointingly, the reaction of *C*,*C*-dialkyl malonic acid monoester **1f** with carbodiimide **2b** (Scheme 1), followed by treatment with NaOH, did not afford the desired barbiturate **4d** but the carboxylic acid **13**.

In this case, the *N*-acylurea intermediate **12** is probably too sterically hindered to undergo cyclization before hydrolysis of the ethyl ester occurs. In fact, by performing only the first step of the process we could recover the *N*-acylurea **12**, which was subsequently cyclized by treatment with NaH in dry DMF affording the target barbiturate **4d**.

Three-Component Sequential Synthesis of 1,3,5,5-Substituted Barbiturates Using the NaOH/Dioxane Protocol. According to the above-described two-step sequential process, the cyclization step produces a barbituric carbanion that can be quenched either by protic acids, affording the corresponding *C*-monosubstituted barbiturates **11a**−**t**, or by alkylating agents, producing fully substituted barbiturates through a three-component sequential process. The results obtained in the latter process are outlined in Table 2.

Unfortunately, the addition of electrophiles after the cyclization step did not prove to be a general entry to the target 1,3,5,5-tetrasubstituted barbiturates **4**. In fact, the carbanions of barbiturates derived from addition of *N*-alkyl,*N*′-aryl carbodiimide **2c** to *C*-aryl malonate **1a** resulted to be very stable and failed to react even with benzyl bromide (**14a**) (entry 1, Table 2), affording the corresponding intermediate *C*-monosubstitued barbiturate **11c**. However, *C*-monoalkyl or unsubstituted malonates and *N*-alkyl,*N*′-aryl carbodiimides bearing *N*-"neutral" or *N*-electron-rich aromatic substituents reacted in the presence of benzyl bromides affording satisfactory yields of 1,3,5,5-tetrasubstituted barbiturates, like the 5-benzyl barbiturates **4a,b,d** (entries 2, 3, 9, respectively) or the 5,5-dibenzyl barbiturate **4g** (entry 12). The sequential process worked well also with other benzyl bromides such as *p*-CF_3 benzyl bromide **14b** (entry 4), *p*-Br benzyl bromide **14e** (entry 10), and fluorenyl bromide **14f** (entry 11). Other rather reactive halides, such as allyl bromide **14c** and methyl iodide **14d**, did not react even with quite nucleophilic 5-alkyl barbituric carbanions (entries 5 and 6 respectively).[24] Barbiturates derived from the electron-poor *N*-aryl carbodiimide **2e** or from the *N*,*N*′-diaryl carbodiimide **2f** failed to react even with **14a** probably because the resulting carbanions are too stabilized (entries 7 and 8, respectively). Finally, *N*,*N*′-dialkyl barbiturates resulted to be much more reactive than barbiturates bearing one or two aromatic rings. In fact, *N*,*N*′-dialkyl barbiturates derived from both *C*-aryl malonate **1a** (entries 13 and 15) and *C*-alkyl malonate **1d** (entry 17) reacted with **14a** affording fully substituted barbiturates **4 h,j,l** in good overall yields. Surprisingly, the reaction worked smoothly even with **14c** (entries 14, 16, 18) which did not react with any of the other barbiturates shown above.

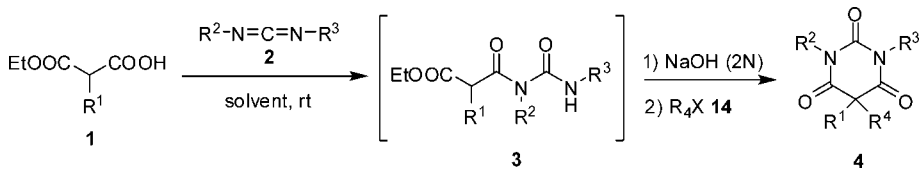
Three-Component Sequential Synthesis of 1,3,5,5-Substituted Barbiturates Using the K_2CO_3/CH_3CN Protocol. Although the protocol above allows for the preparation of different fully substituted barbiturates, it presents some limitations. In order to expand the scope of the process we decided to investigate a new, more flexible protocol for the one-pot cyclization/alkylation steps in order to prepare a larger array of barbiturates. First of all, we sought to find a more general method for the C-alkylation of barbiturates that would work not only with highly electrophilic benzyl halides. Surprisingly, in literature we could not find any simple general procedure. Thus, after screening several combinations of solvents and bases we were able to find a suitable procedure consisting in the use of a suspension of anhydrous K_2CO_3 in acetonitrile in a sealed tube at 120 °C (Table 3).

Following this procedure, *N*-alkyl,*C*,*N*′-diaryl trisubstituted barbiturates such as **11b**,**d**, which were unreactive even with **14a** under the NaOH/dioxane protocol, afforded the fully substituted barbiturates **4aa** and **4ab,** respectively, in good yields (entries 1 and 2, Table 3) upon alkylation with ethyl iodide **14g**. As expected, even the more nucleophilic barbiturate **11g** reacted

(23) It should be noted that in this case the cyclization step resulted to be much slower (overnight compared to 10 min). However, this should be ascribed not only to the different conditions but also to the fact that in such reaction the rate-determining step is the deprotonation step, which is less favored when the two nitrogens are substituted with two electron-donating groups such as alkyl groups: Xin, Z.; Pei, Z.; von Geldem, T.; Jirousek, M. *Tetrahedron Lett.* **2000**, *41*, 1147–1150.

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

TABLE 2. Three-Component Sequential Synthesis of 1,3,5,5-Substituted Barbiturates 4 Using the NaOH/Dioxane Protocol



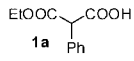
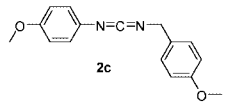
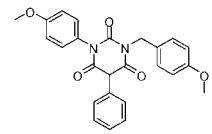
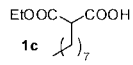
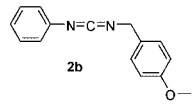
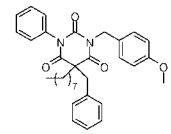
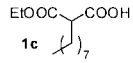
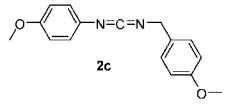
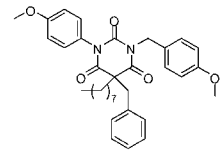
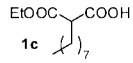
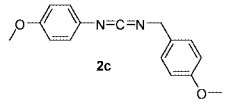
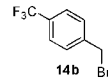
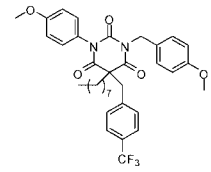
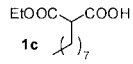
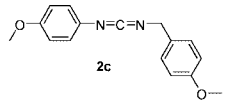
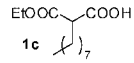
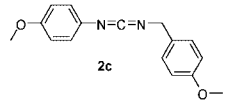
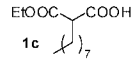
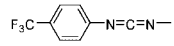
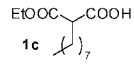
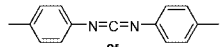
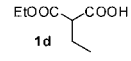
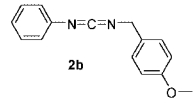
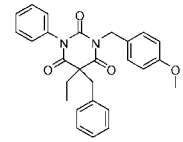
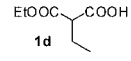
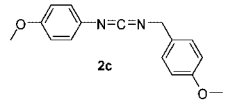
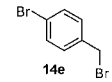
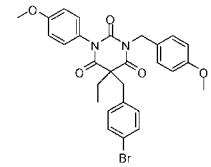
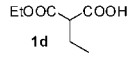
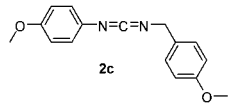
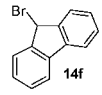
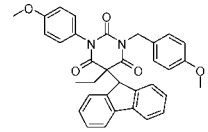
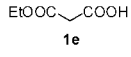
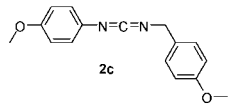
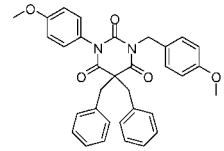
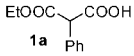
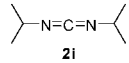
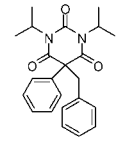
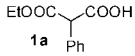
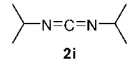
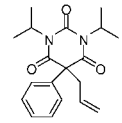
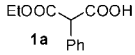
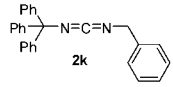
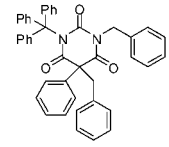
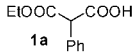
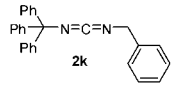
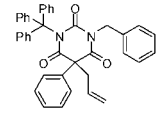
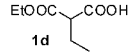
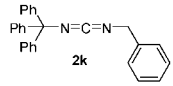
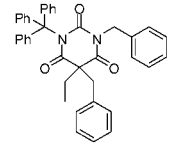
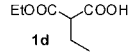
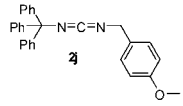
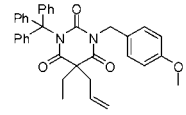
Entry	Malonic acid	Carbodiimide	Alkyl alide	Barbiturates	Product, yield (%)
1					**11c**, 80[a]
2					**4a**, 63
3					**4b**, 63
4					**4c**, 60
5				/	n.r.[a]
6				/	n.r.[a]
7				/	n.r.[a]
8				/	n.r.[a]
9					**4d**, 67
10					**4e**, 62

TABLE 2. Continued

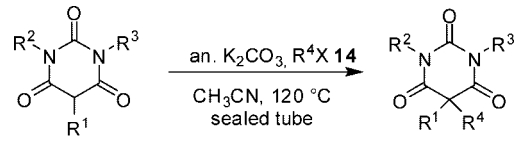
Entry	Malonic acid	Carbodiimide	Alkyl alide	Barbiturates	Product, yield (%)
11	 **1d**	 **2c**	 **14f**		**4f**, 65
12	 **1e**	 **2c**	 **14a**		**4g**, 58
13	 **1a**	 **2i**	 **14a**		**4h**, 65
14	 **1a**	 **2i**	 **14c**		**4i**, 63
15	 **1a**	 **2k**	 **14a**		**4j**, 65
16	 **1a**	 **2k**	 **14c**		**4k**, 45
17	 **1d**	 **2k**	 **14a**		**4l**, 60
18	 **1d**	 **2j**	 **14c**		**4m**, 58

[a] The alkylation step did not occurr.

smoothly with alkyl halides, such as octyl bromide **14h**, effectively leading to the formation of the barbiturate **4ac** (entry 3). The versatility of the K_2CO_3/CH_3CN alkylation protocol is further demonstrated by the fact that even *N*,*N*′-diaryl barbiturates **11l** and **11n** reacted with **14g** affording the desired barbiturates **4ae** and **4af** in good yields (entries 5 and 6). As the only exception, *C*,*N*,*N*′-triaryl barbiturates such as **11j**, did not react in these conditions. However, the alkylated barbiturate **4ad** was obtained in good yield (entry 4, Table 3) performing the reaction in DMF at 80 °C. The three components one-pot sequential process for the synthesis of fully substituted barbiturates (see Table 2) was therefore adapted to the optimized alkylation conditions with K_2CO_3/CH_3CN (Table 4).

The malonate **1a** underwent three-component reaction with the electron-rich carbodiimide **2c** and benzyl bromide **14a** (entry 1, Table 4), allyl bromide **14c** (entry 2), and even with the less reactive propyl iodide **14g** (entry 3, Table 4) producing the *C*-disubstituted barbiturates **4ag**−**ai**, respectively, in very good yields. The process worked well even when malonates **1a** and **1b** were reacted with the "neutral" carbodiimide **2b** and 1-iodohexane **14i** (entries 4 and 5), producing the barbiturates **4aj** and **4ak**, respectively, in reasonable yields. However, **1a** and the

TABLE 3. Alkylation of Barbituric Acids 11



11 **4**

entry	barbituric acid	R^1	R^2	R^3	R^4	product	yield (%)
1	**11b**	Ph	Ph	PMB	CH_3CH_2I, **14g**	**4aa**	73
2	**11d**	biphenyl	Ph	PMB	CH_3CH_2I, **14g**	**4ab**	65
3	**11g**	*n*-octyl	Ph	PMB	$CH_3(CH_2)_7Br$, **14h**	**4ac**	78
4	**11j**	Ph	*p*-Tol	*p*-Tol	$CH_3(CH_2)_5I$, **14i**	**4ad**	68[a]
5	**11l**	*n*-octyl	*p*-Tol	*p*-Tol	CH_3CH_2I, **14g**	**4ae**	94
6	**11n**	*n*-octyl	4-NO_2-Ph	PMP	CH_3CH_2I, **14g**	**4af**	75

[a] Reaction performed in DMF at 80 °C.

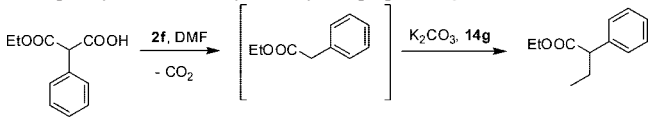
electron-poor carbodiimide **2e** underwent reaction only with **14c**, affording the fully substituted barbiturate **4al** (entry 6), whereas with **14g** (entry 7) we did not observe the formation of the desired barbiturate. The more reactive 2-octyl malonate **1c**, instead, gave the desired 5,5-dialkylated barbiturates in all cases when reacted with *N*-alkyl,*N*′-aryl carbodiimides. Thus, **1c** reacted smoothly with the electron-rich carbodiimide **2c** and alkyl halides **14g** and **14j**, affording the barbiturates **4am** and **4an**, respectively, in excellent yields (entries 8 and 9). Even the electron-poor carbodiimide **2e**, which failed in the three-component process with *C*-aryl malonates such as **1a**, reacted successfully with **1c** and allyl bromide **14c**, iodo propane **14g** and 3-phenethyl bromide **14k** affording the *C*,*C*-disubstituted barbiturates **4ao**, **4ap**, and **4aq**, respectively, in good yields, (entries 10−12). Unsubstituted malonate **1e** underwent four-component one-pot sequential process when reacted with carbodiimides **2b,c** and alkyl bromides **14j** affording *C*-disubstituted barbiturates **4ac** (entry 14) and **4an** (entry 13), respectively, in acceptable yields. Unfortunately, the three-component process did not work when performed with *N*,*N*′-diaryl carbodiimides, such as **2f** and **2h** (entries 15−17, Table 4). It should be noted, however, that *C*-alkyl and *C*-aryl-*N*,*N*′-diaryl barbiturates can be successfully reacted with alkyl halides giving 5,5-substituted barbiturates in very good yields (see Table 3).[25]

Moreover, starting from carbodiimides with cleavable *N*-substituents, we could synthesize the corresponding *N*-monosubstituted barbiturates **24**. For instance, the trityl group and the *p*-methoxy benzyl group could be easily cleaved forming *N*-alkyl or *N*-aryl monosubstituted barbiturates **24**, respectively (Table 5).

Discussion

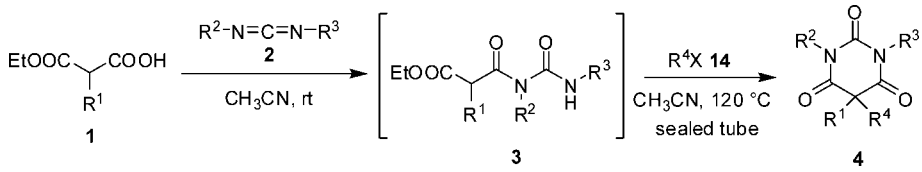
The full reaction sequence of the MC one-pot process leading to 1,3,5,5-substituted barbiturates **4** or 1,3,5-trisubstituted barbiturates **11** is portrayed in Scheme 2.

(25) Because alkylation of *C*,*N*,*N*-triaryl barbituric acids occurred only in DMF at 80 °C (see entry 4, Table 3), we tried to perform the three-component process in such conditions. However, the condensation between carbodiimide **2f** and acid **1a** in DMF afforded exclusively the decarboxylation product, which subsequently underwent alkylation by iodopropane **14g**.



The sequence involves a first proton transfer from the carboxylic acids **1** to the basic nitrogen of the carbodiimide **2** followed by reversible addition of the carboxylate to form the *O*-acyl-isourea intermediate **15**. The latter is a reactive species that, in the absence of a nucleophile, can undergo a rearrangement, the so-called O→N acyl migration, to give *N*-acylurea derivatives **3**. To obtain the formation of **3** in good yield, one should suppress two side processes that could arise when malonic acids such as **1** are used. In fact, it is known that, once formed, malonic carboxylates easily undergo decarboxylation. *C*-Alkyl and, even more, *C*-aryl malonic acid monoethylesteres are prone to decarboxylation when treated with dialkyl carbodiimides such as DIC (see entries 22, 23, 26, Table 1), because these carbodiimides are less electrophilic and the equilibrium leading to **15** is less shifted to the right, thus favoring the loss of CO_2 leading to **16**. In fact when the reaction was carried out with more electrophilic *N*-alkyl,*N*′-aryl or *N*,*N*′-diaryl and even *N*-alkyl,*N*′-trityl carbodiimides, the corresponding *N*-acylureas **3** were formed in good yields. Moreover, the intermediate *O*-acyl-isourea **15** can undergo elimination of urea leading to the formation of the highly reactive ketene **17** that, in the absence of a nucleophile, could react with a molecule of carbodiimide leading to the formation of a [4 + 2] cycloadduct **18**. Again, we observed the formation of **18** as a byproduct only when the reaction was carried out with basic DIC and *C*-monoalkyl malonic acid monoethylesters. However, performing the condensation between DIC and malonic acid monoethylesters in low polarity solvents, such DCM, and in the presence of an equivalent of a base, i.e., TMP, which facilitated the O→N acyl migration process, we were able to suppress almost entirely the formation of **18**, leading to the formation of the *N*-acylureas **3** in good yields (see entries 24, 27, Table 1). *N*-Acylureas **3** could be cyclized and alkylated upon in situ treatment with a base (that should be compatible with the solvent used for their generation), followed by an electrophile, producing a one-pot three-component sequential process leading to the target substituted barbiturates. Two different protocols were explored, namely, a "soft" protocol consisting in the treatment with aqueous 2 N NaOH in dioxane at room temperature and a "hard" protocol consisting in the use of anhydrous K_2CO_3 in CH_3CN at high temperature. The choice of the most appropriate protocol depends on the reactivity of the electrophile and of the resulting carbanion **20**, which is strongly stabilized by the two adjacent carbonyl groups. Moreover, the nucleophilicity of **20** depends on (1) the substituents on the nitrogen atoms and (2) the substituent R^1. When such substituents are electron-withdrawing

TABLE 4. Three-Component Sequential Synthesis of 1,3,5,5-Substituted Barbiturates 4 with the K_2CO_3/CH_3CN Protocol



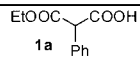
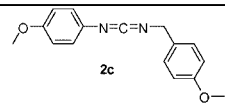
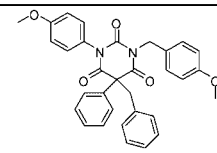
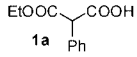
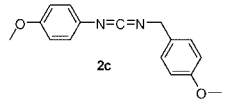
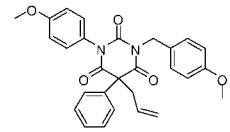
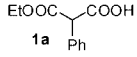
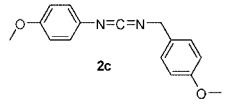
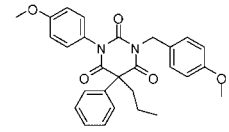
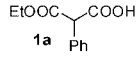
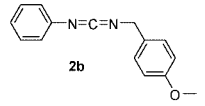
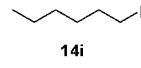
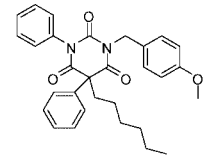
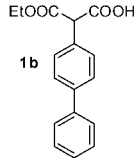
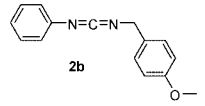
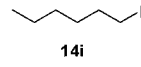
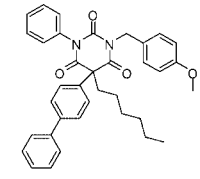
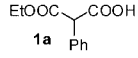
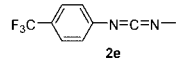
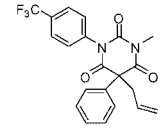
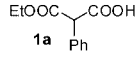
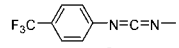
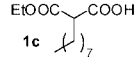
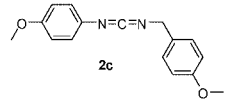
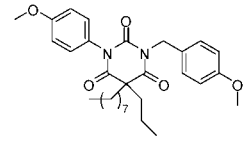
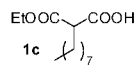
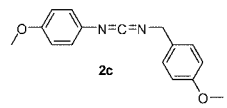
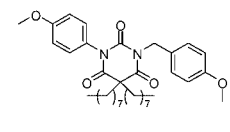
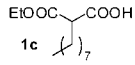
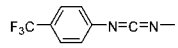
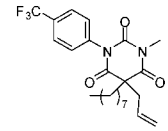
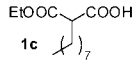
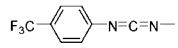
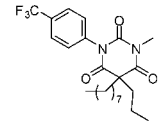
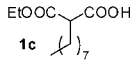
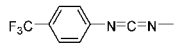
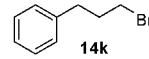
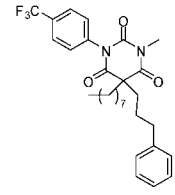
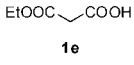
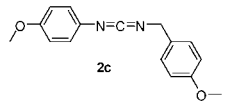
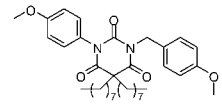
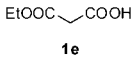
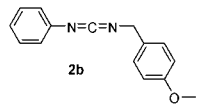
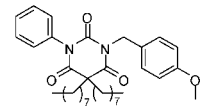
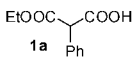
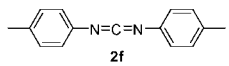
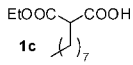
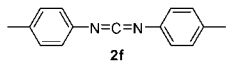
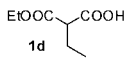
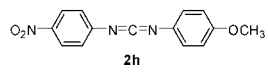
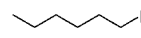
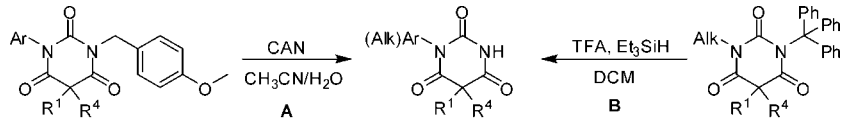
Entry	Malonic acid	Carbodiimide	Alkyl alide	Barbiturates	Product, yield (%)
1					**4ag**, 71
2					**4ah**, 70
3					**4ai**, 52
4					**4aj**, 55
5					**4ak,** 56
6					**4al**, 67
7				/	n.r.[a]
8					**4am**, 80
9					**4an,** 73

TABLE 4. Continued

Entry	Malonic acid	Carbodiimide	Alkyl alide	Barbiturates	Product, yield (%)
10	 1c	 2e	 14c		**4ao,** 90
11	 1c	 2e	 14g		**4ap**, 65
12	 1c	 2e	 14k		**4aq**, 61
13	 1e	 2c	 14j		**4an**, 45
14	 1e	 2b	 14j		**4ac**, 42
15	 1a	 2f	 14g	/	n.r.[b]
16	 1c	 2f	 14g	/	n.r.[c]
17	 1d	 2h	 14i	/	n.r.[c]

[a] Alkylation did not occur. [b] Degradation of the starting material occurred during the alkylation step. [c] The cyclization step failed.

TABLE 5. Synthesis of *N*-Monosubstituted Barbiturates 24

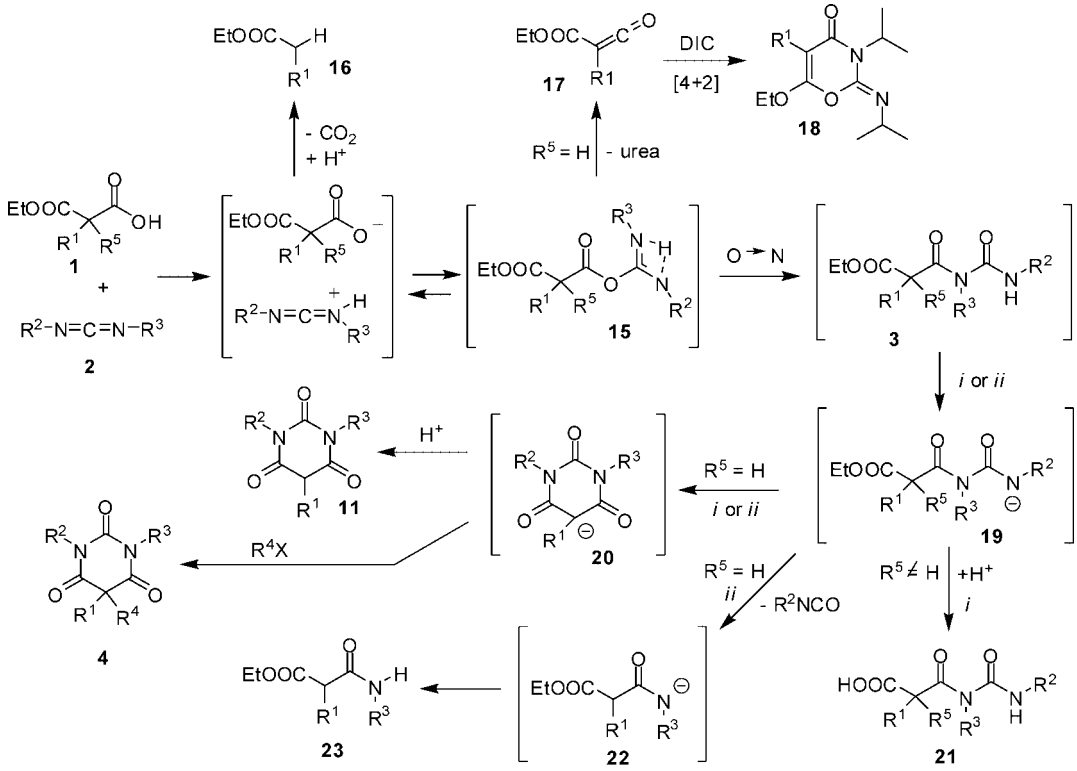


4 24 4

entry	barbiturate	R^1	R^4	Ar or Alk	method	product	yield (%)
1	**4a**	*n*-octyl	benzyl	Ph	A	**24a**	76
2	**4aa**	Ph	ethyl	Ph	A	**24b**	85
3	**4ak**	biphenyl	*n*-hexyl	Ph	A	**24c**	82
4	**4j**	Ph	benzyl	benzyl	B	**24d**	92
5	**4k**	Ph	allyl	benzyl	B	**24e**	89
6	**4l**	ethyl	benzyl	benzyl	B	**24f**	93

aromatic rings, the negative charge is further stabilized rendering **20** even less nucleophilic. Thus, barbiturates derived from *N*,*N*′-dialkyl carbodiimides are more nucleophilic than those derived from *N*-alkyl,*N*′-aryl carbodiimides, which in turn are more

SCHEME 2. Mechanism of the Three-Component Sequential Process



i NaOH (2N), dioxane, rt; *ii* an. K_2CO_3, CH_3CN, 120 °C

nucleophilic than *N*,*N*′-diaryl barbiturates. Accordingly, 5-alkyl barbiturate carbanions having at least one *N*-alkyl group were able to react only with highly electrophilic benzyl halides using the "soft" protocol, whereas more stabilized 5-aryl derivatives were unreactive. It is worth nothing that *N*,*N*′-dialkyl barbiturates, independently of the nature of the R^1 substituent, could be alkylated with both benzyl and allyl bromides following the "soft" protocol (see entries 13−18, Table 2). Barbiturates derived from *N*,*N*′-diaryl carbodiimides could not be alkylated by means of the "soft" protocol. However, all of the barbiturate carbanions could be C-alkylated using the "hard" protocol, regardless of the *N*-substituents, with a wide range of alkyl halides providing a general method for the synthesis of fully substituted barbiturates (see Table 3). Unfortunately, when the one-pot sequential process was carried out according to the "hard" protocol, we discovered that the cyclization step failed with *N*,*N*′-diaryl substrates (see Table 4). In these cases the anion **19** (Scheme 2) is likely to be too stable to undergo sufficiently rapid cyclization, and therefore elimination of the corresponding isocyanate becomes competitive, leading to the formation of the amide **23**. However, this is not a big limitation because the corresponding *N*,*N*′-diaryl barbiturates could be easily synthetizated through a stepwise process, namely, the synthesis of the *C*-monosubstituted barbiturate through the "soft" NaOH protocol, and chromatographic isolation followed by alkylation, using the "hard" protocol (K_2CO_3 in CH_3CN, 120 °C, or DMF at 80 °C for *N*,*N*′-diaryl-*C*-aryl barbiturates) (see Table 3). In all other cases, the three-component one pot sequential process produced the desired fully substituted barbiturates in good yields.

Conclusions

In summary, we have developed a general, straightforward, and high-yielding method for the preparation of a large array of 1,3,5-trisubstituted barbiturates, using mild conditions exploiting a one-pot sequential process starting from easily accessible starting materials such as carbodiimides and *C*-monosubstituted malonic acids monoethylesteres. We have also studied in detail the reactivity of the target barbiturates toward alkyl halides, which was found to be strongly dependent on the stabilization of the barbituric carbanion intermediates and therefore on the malonic acids substituent R^1 as well as on the *N*-substituents R^2 and R^3. By combining the two processes, namely, the cyclization and the C-alkylation, we have finally developed two different protocols for the combinatorial synthesis of 1,3,5,5-tetrasubstituted barbiturates through a three-component one-pot sequential process. A large array of structurally diverse barbiturates can be synthesized through this method, which appears particularly suitable for solid phase/combinatorial chemistry.

Experimental Section

General Procedure for the Synthesis of 1,3,5-Substituted Barbiturates 11. To a stirred solution of malonic acid monoesters **1** (1 equiv) in dioxane (0.1 M solution) was added carbodiimide **2** (1.1 equiv), and the mixture was stirred at room temperature overnight. A 2 N aqueous NaOH solution was added, and when the cyclization was complete (typically 10 min, TLC monitoring), a 1 N aqueous HCl solution was added until acidic pH was reached. The mixture was extracted with AcOEt; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by flash chromatography affording **11**.

When DIC was used as the carbodiimide component, the reaction was carried out in DCM in the presence of 1 equiv of TMP, and the cyclization step was run overnight.

1-Cyclohexyl-3,5-diphenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 11a. R_f = 0.48 (hexane/AcOEt = 70:30); FTIR (nujol) ν 1711,

1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 8H), 7.16 (m, 2H), 4.76 (s, 1H), 4.66 (m, 1H), 2.31 (m, 1H), 2.26 (m, 1H), 1.81 (m, 2H), 1.65 (m, 3H), 1.33 (m, 2H), 1.18 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.3, 166.9, 151.2, 134.4, 133.5, 129.6, 129.4, 129.1, 128.9, 128.3, 127.3, 56.8, 56.0, 29.6, 28.5, 26.3, 26.1, 25.0; ESI (*m/z*) 385.1 [M^+ + Na, (48)], 363.2 [M^+ + 1, (100)]; HRMS calcd for [$C_{22}H_{22}N_2O_3$] 362.1625, found 362.1629.

General Procedure for the Synthesis of 1,3,5,5-Substituted Barbiturates 4 under NaOH\Dioxane Protocol. To a stirred solution of malonic acid monoesters **1** (1 equiv) in dioxane (0.1 M solution) was added carbodiimide **2** (1.1 equiv), and the mixture was stirred at room temperature overnight. A 2 N aqueous NaOH solution was added, followed by neat benzyl halide **14** (4 equiv) upon completion of the cyclization (typically 10 min, TLC monitoring). After 1 h the solution was acidified with a 1 N aqueous HCl solution and extracted with AcOEt; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by flash chromatography affording **4**.

5-Benzyl-5-ethyl-1-(4-methoxybenzyl)-3-phenyl-pyrimidine-2,4,6-trione 4d. R_f = 0.45 (hexane/AcOEt = 80:20); FTIR (nujol) ν 1698, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.33 (d, J = 7.6 Hz, 2H), 7.22 (m, 1H), 7.11 (m, 2H), 6.95 (d, J = 7.9 Hz, 2H), 6.83 (d, J = 7.6 Hz, 2H), 6.81 (m, 1H), 4.98 (d, J = 13.7 Hz, 1H), 4.86 (d, J = 13.7 Hz, 1H), 3.81 (s, 3H), 3.38 (d, J = 12.7 Hz, 1H), 3.24 (d, J = 12.7 Hz, 1H), 2.28 (m, 2H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5, 171.0, 159.3, 135.0, 134.5, 131.0, 129.5, 129.3, 129.0, 128.6, 128.3, 128.2, 127.6, 113.8, 59.7, 55.3, 46.1, 44.8, 33.3, 9.7; ESI (*m/z*) 465.2 [M^+ + Na, (100)], 443.1 [M^+ + 1, (87)]; HRMS calcd for [$C_{27}H_{26}N_2O_4$] 442.1886, found 442.1883.

General Procedure for the Alkylation of Barbiturates 11 to 4. A suspension of barbituric acid **11** (1 equiv), anhydrous K_2CO_3 (1.2 equiv), and alkyl halide **14** (2.1 equiv) in CH_3CN (0.1 M solution respect to the acid) was charged in a sealed tube and heated at 120 °C. When the starting material disappeared (TLC monitoring) the temperature was lowered to room temperature, water was added, and the mixture was extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, and the crude purified by flash chromatography affording **4**.

In the case of *C*-aryl barbituric acids **11** bearing two aromatics at the nitrogen atoms, the reaction was carried out in DMF at 80 °C.

General Procedure for the Synthesis of 1,3,5,5-Substituted Barbiturates 4 under the K_2CO_3/CH_3CN Protocol. In a sealed tube, carbodiimide **2** (1.1 equiv) was added to a stirred solution of malonic acid monoester **1** (1 equiv) in CH_3CN (0.1 M solution), and the mixture was stirred at room temperature overnight. Solid anhydrous K_2CO_3 (2.1 equiv) followed by alkyl halide **14** (4 equiv) was added, and the mixture was heated at 120 °C. After the reaction was complete (typically 30 min for highly reactive benzyl or allyl halides and 12 h for less reactive alkyl halides, TLC monitoring), the mixture was cooled to room temperature, and water was added. The mixture was extracted with AcOEt; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by flash chromatography affording **4**.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-5-octyl-5-propyl-pyrimidine-2,4,6-trione 4am. R_f = 0.60 (hexane/AcOEt = 80:20); FTIR (nujol) ν 1699, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 5.07 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.02 (m, 2H), 1.18 (m, 14H), 0.89 (t, J = 7.0 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.1, 172.0, 159.8, 159.3, 151.0, 130.8, 129.3, 128.6, 127.2, 114.7, 113.8, 57.0, 55.5, 55.2, 44.7, 42.3, 40.6, 31.7, 29.4, 29.1, 29.0, 25.0, 22.6, 18.5, 14.0, 13.9; ESI (*m/z*) 531.3 [M^+ + Na, (100)], 509.3 [M^+ + 1, (98)]; HRMS calcd for [$C_{30}H_{40}N_2O_5$] 508.2927, found 508.2032.

General Procedure for the *N*-PMB Deprotection of 4 to 24. To a solution of the barbiturate **4** (1 equiv) in CH_3CN (0.1 M solution) was added a solution of CAN (4 equiv) in water (0.8 M solution) dropwise at 0 °C. The temperature was raised to room temperature, and when the starting material disappeared (TLC monitoring) the mixture was diluted with water and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum, and the crude was purified by flash chromatography to give **24**.

5-Benzyl-5-octyl-1-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 24a. R_f = 0.43 (hexane/AcOEt = 80:20); FTIR (nujol) ν 3250, 1707, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.42 (m, 3H), 7.32 (m, 3H), 7.16 (m, 2H), 6.85 (m, 2H), 3.37 (d, J = 13.0 Hz, 1H), 3.29 (d, J = 13.0 Hz, 1H), 2.30 (m, 2H), 1.28 (m, 12H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.8, 171.3, 148.7, 134.8, 133.6, 129.6, 129.4, 129.2, 128.8, 128.2, 128.0, 59.3, 45.8, 39.5, 31.8, 29.5, 29.2, 29.1, 25.5, 22.6, 14.1; ESI (*m/z*) 429.2 [M^+ + Na, (100)], 407.2 [M^+ + 1, (48)].

General Procedure for the *N*-Trityl Deprotection of 4 to 24. To a solution of barbiturate **4** (1 equiv) in DCM (0.025 M solution) was added Et_3SiH (4 equiv) at room temperature followed by TFA (0.25% in volume). When the starting material disappeared (TLC monitoring) a 5% $NaHCO_3$ aqueous solution was added until basic pH was reached. The mixture was extracted with DCM; the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum; and the crude was purified by flash chromatography affording **24**.

1,5-Dibenzyl-5-phenylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione 24d. R_f = 0.25 (hexane/AcOEt = 80:20); FTIR (nujol) ν 3124, 1715, 1696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.34 (m, 5H), 7.26−7.10 (m, 10H), 4.95 (s, 2H), 3.80 (s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.7, 169.9, 149.4, 137.9, 135.9, 135.2, 130.6, 129.6, 129.1, 128.9, 128.8, 128.2, 127.8, 126.8, 62.7, 45.2, 42.6; ESI (*m/z*) 407.5 [M^+ + Na, (21)], 385.2 [M^+ + 1, (100)].

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

Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra for compounds **1**, **2**, **3**, **4**, **11**, and **24**. Characterization data for compounds **1a**−**f**, **2a**−**k**, **3a,j,p,r,s,u**, **4a**−**c,e**−**m,aa**−**al,an**−**ar**, **11b**−**u**, and **24a**−**c,e**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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