Tetrahedron Letters 53 (2012) 4733–4737

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Three-component sequential synthesis of *N,N′*-disubstituted 5-arylidenedihydropyrimidine-2,4-dione

Maria Cristina Bellucci [a], Alessandro Volonterio [b,*]

[a] *Dipartimento di Scienze Molecolari Agroalimentari, Università degli Studi di Milano, via Celoria 2, 20133 Milano, Italy*
[b] *Department of Chemistry, Materials and Chemical Engineer 'Giulio Natta', Politecnico di Milano, via Mancinelli 7, 20131 Milano, Italy*

ARTICLE INFO

Article history:
Received 23 May 2012
Revised 19 June 2012
Accepted 25 June 2012
Available online 29 June 2012

Keywords:
Multi-component
Sequential synthesis
Carbodiimides
Dihydropyrimidine-2,4-dione
N-Acylurea

ABSTRACT

A three-component sequential process consisting in (1) in situ formation of carbodiimides by Staudinger reaction, (2) reaction with 2-(bromomethyl)-3-aryl-2-propenoic acids, and (3) final cyclization of the resulting *N*-acylurea intermediates in order to obtain the synthesis of an array of *N,N′*-disubstituted 5-arylidenedihydropyrimidine-2,4-dione under mild conditions is presented.

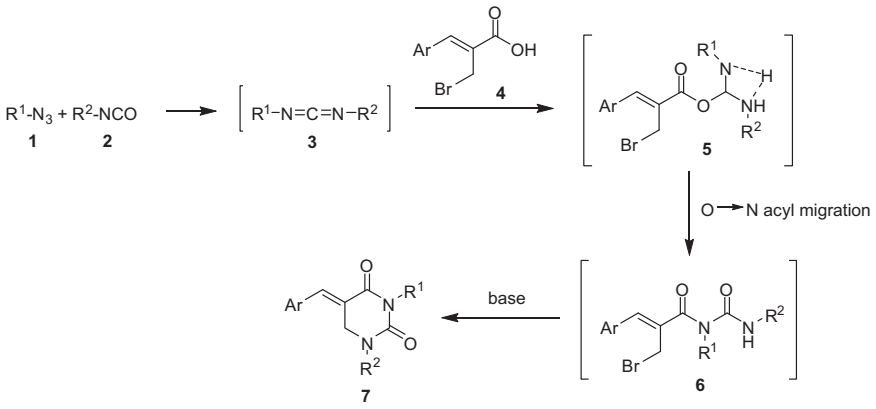
The development of a new multi-component (MC) coupling process has attracted intense interest in recent years.[1] Such processes allow the efficient construction of elaborate molecules from simple precursors in a minimum numbers of steps, and many are ideally suited for the generation of structurally diverse libraries of small molecules. In particular, 'one-pot' MC sequential synthesis features a high degree of reaction mass efficiency, thus playing a central role in the development of modern synthetic methodology for pharmaceutical and drug discovery programs.[2] This is particularly true for the synthesis of heterocycles. Indeed, many small synthetic molecules with high medicinal potential contain heterocyclic rings. However, the range of easily accessible and suitably functionalized heterocyclic building blocks is surprisingly limited and the construction of even a small array of relevant heterocyclic compounds is far from trivial.[3] Thus, one of the challenges of medicinal chemistry is the promotion of the structural diversity of a ligand, which can be achieved by the attachment of pharmacophoric groups to the rigidified molecule. Small, substituted heterocyclic compounds offer a unique possibility of different kinds and degrees of substitution. In particular, pyrimidine-2,4-diones are a class of bioactive molecules which have attracted considerable attention in the pharmaceutical industry as anti-inflammatory agents,[4] dopamine receptor antagonists,[5] serotonin uptake inhibitors,[6] and antiepileptic agents.[7] This moiety is also the core structural element of some fungicides[8] and herbicides.[9] The observed activities usually do not arise from the heterocycle itself, but from the different ligands that have been attached to it. For this reason there is a lot of interest in developing new strategies for a straightforward synthesis of substituted pyrimidine-2,4-diones, overall if milder than the most utilized strategies used to prepare such scaffolds which rely on the strongly acidic or basic cyclization of β-ureidopropionic acids[10] or by hydrogenation of the corresponding uracils. [11]

As a part of a project aimed at developing new MC domino process for the synthesis of small heterocycles and glyco-conjugates by using in situ generated carbodiimides and suitable carboxylic acids,[12] we wish to report the straightforward regioselective domino synthesis of *N,N′*-disubstituted-5-arylidendihydropyrimidine-2,4-diones **7** under mild conditions (room temperature, avoiding the use of strong acids/bases), starting from easily accessible 2-(bromomethyl)-3-aryl-2-propenoic acids **4** (Scheme 1). The reaction sequence involves the synthesis in situ of the reacting carbodiimide **3** through Staudinger reaction starting from the corresponding azides **1** and isocyanates **2**, followed by the addition of acids **4** into the reaction mixture which leads to the formation of *N*-acylurea derivatives **6** through the O→N acyl migration rearrangement of the corresponding *O*-acylisourea intermediates **5**. Finally, in situ addition of a suitable base triggers the cyclization to the final *N,N′*-disubstituted-5-arylidendihydropyrimidine-2,4-diones **7**.

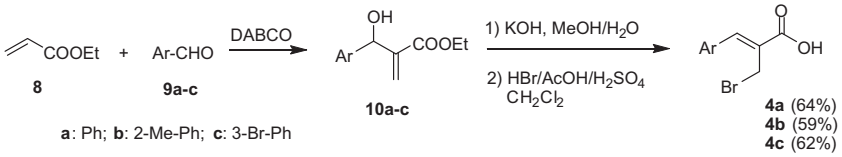
The starting 2-(bromomethyl)-3-aryl-2-propenoic acids **4** were easily synthesized by Baylis–Hillman reaction[13] of ethyl acrylate **8** and aromatic aldehydes **9a–c**, followed by hydrolysis of the ester function and bromination with a HBr solution (Scheme 2).[14]

* Corresponding author. Tel.: +39 02 23993139; fax: +39 02 23993180.
E-mail address: alessandro.volonterio@polimi.it (A. Volonterio).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.109



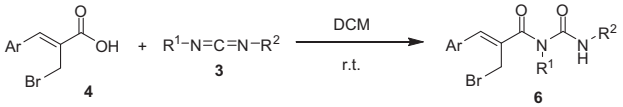
Scheme 1. Synthesis of *N*,*N*′-disubstituted-5-arylidendihydropyrimidine-2,4-diones **7**.



Scheme 2. Synthesis of 2-(bromomethyl)-3-aryl-2-propenoic acids **4**.

With the acids **4** in hand, we began to study their reactivity in the presence of carbodiimides **3** (Table 1). Acids **4a–c** resulted to be highly reactive and prone to undergo side reactions, such as decarboxylation and subsequent formation of byproducts, when the reaction is carried out in the presence of a base, such as 2,4,6-trimethylpyridine (TMP, generally used in this kind of reactions)[12] and polar solvents such as dioxane or acetonitrile.[15] However, when dichloromethane (DCM) is used, the process furnished the clean formation of *N*-acylurea derivatives **6** in high yields unless highly basic carbodiimides were used. Indeed, when acid **4a** was reacted with *N*,*N*′-dialkylcarbodiimides, such as commercially available DIC **3a** and DCC **3b**, we obtained the formation of a mixture of uncharacterized byproducts which likely arises from decarboxylation of the starting acid due to the high basicity of such carbodiimides (Table 1, entries 1 and 2, respectively). Less basic 'strongly asymmetric'[12b] carbodiimides, namely carbodiimides bearing an aryl and an alkyl substituent, such as *N*-benzyl, *N*′-phenyl carbodiimide **3c**, reacted smoothly with acid **4a** producing the corresponding *N*-acyl urea **6a** in high yield and, gratifyingly, as the only regioisomer (Table 1, entry 3). The reaction worked efficiently also with 2-(bromomethyl)-3-aryl-2-propenoic acids with different substitution at the aromatic ring, such as methyl- and bromo-derivatives **4b**,**c**, leading to the regiospecific formation of compounds **6b**,**c**, respectively, in high yields (Table 1, entries 4 and 5). To our surprise 'weakly asymmetric'[12b] *N*,*N*′-dialkylcarbodiimides, namely carbodiimides bearing two alkyl substituents very different in terms of bulkiness, such as *N*-*tert*-butyl, *N*′-phenethyl carbodiimide **3d**, did not promote the decarboxylation of the

Table 1
Synthesis of *N*-acylurea derivatives **6**



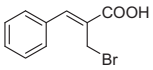
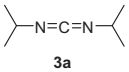
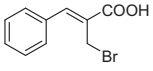
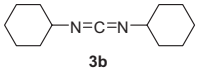
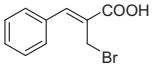
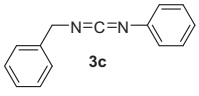
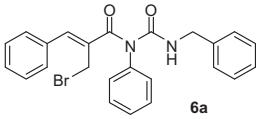
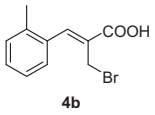
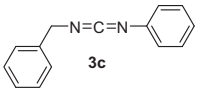
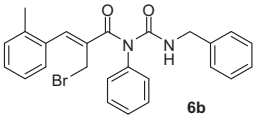
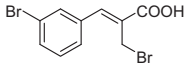
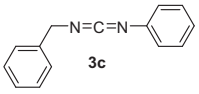
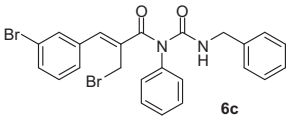
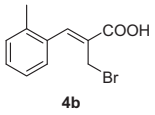
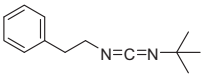
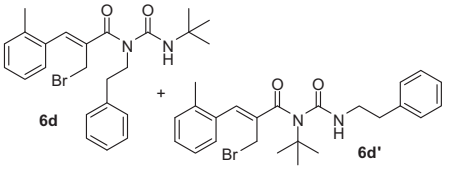
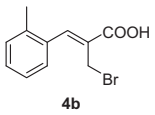
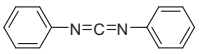
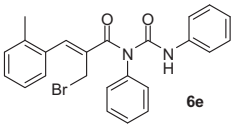
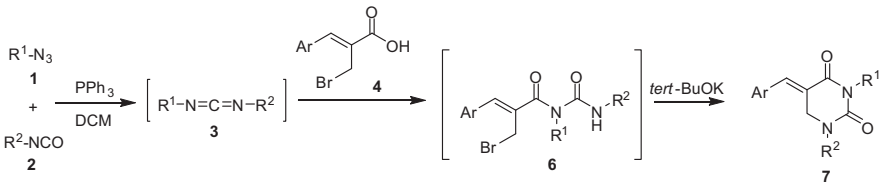
Entry	Ar	Acid	R^1	R^2	Carbodiimide	Product	Yield[a] (%)
1	Ph	 **4a**	*i*-Pr	*i*-Pr	 **3a**	/	n.r.[b]
2	Ph	 **4a**	*cyclo*-Hex	*cyclo*-Hex	 **3b**	/	n.r.[b]
3	Ph	 **4a**	Ph	Bn	 **3c**	 **6a**	88

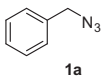
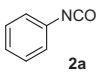
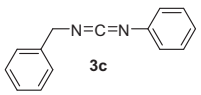
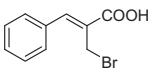
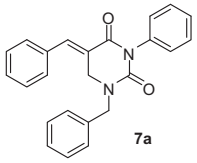
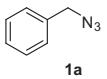
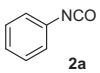
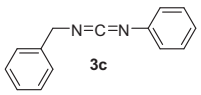
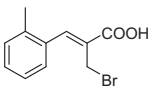
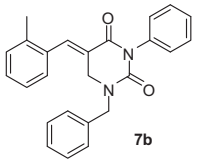
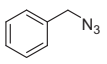
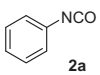
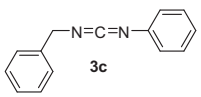
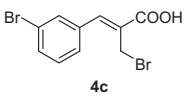
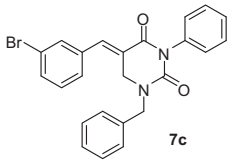
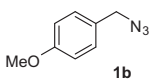
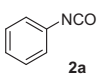
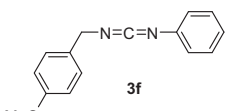
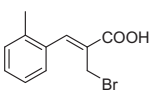
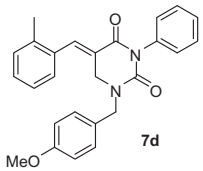
Table 1 (*continued*)

Entry	Ar	Acid	R^1	R^2	Carbodiimide	Product	Yield[a] (%)
4	2-Me-Ph	 **4b**	Ph	Bn	 **3c**	 **6b**	95
5	3-Br-Ph	 **4c**	Ph	Bn	 **3c**	 **6c**	85
6	2-Me-Ph	 **4b**	*tert*-Bu	$-(CH_2)_2$-Ph	 **3d**	 **6d** + **6d'**	84[c]
7	Ph	 **4b**	Ph	Ph	 **3e**	 **6e**	92

[a] Isolated yields.
[b] No reaction. The formation of byproducts was detected.
[c] Equimolecular mixture of the two diastereoisomers.

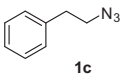
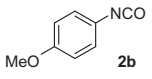
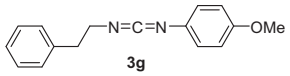
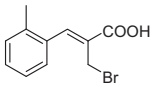
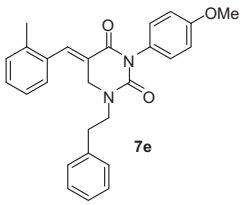
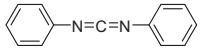
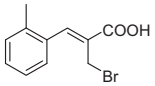
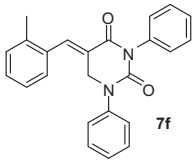
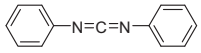
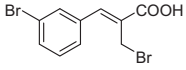
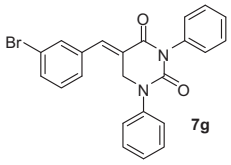
Table 2
One-pot multi-component sequential synthesis of *N*,*N*′-disubstituted-5-arylidendihydropyrimidine-2,4-diones **7**



Entry	R^1N_3	R^2-NCO	Carbodiimide	Acid	Product	Yield[a] (%)
1	 **1a**	 **2a**	 **3c**	 **4a**	 **7a**	77
2	 **1a**	 **2a**	 **3c**	 **4b**	 **7b**	79
3	 **1a**	 **2a**	 **3c**	 **4c**	 **7c**	73
4	 **1b**	 **2a**	 **3f**	 **4b**	 **7d**	68

(*continued on next page*)

Table 2 (*continued*)

Entry	R^1N_3	R^2-NCO	Carbodiimide	Acid	Product	Yield[a] (%)
5	 **1c**	 **2b**	 **3g**	 **4b**	 **7e**	75
6	 **1d**	 **2a**	 **3e**	 **4b**	 **7f**	64
7	 **1d**	 **2a**	 **3e**	 **4c**	 **7g**	70

[a] Overall yields.

starting acid **4a**. However, the reaction was not regioselective at all, producing a 1:1 mixture of the two regioisomers **6d**, **6d′** although in high yields (Table 1, entry 6).[16] Finally, acid **4b** reacted efficiently also with *N,N′*-diaryl carbodiimide, such as *N,N′*-diphenyl carbodiimide **3e**, giving the formation of the corresponding *N*-acyl urea derivative **6e** in high yields (Table 1, entry 7).

Next, we investigated the use of a suitable base to trigger the cyclization in situ, thus in DCM as solvent, in order to obtain the target *N,N′*-disubstituted-5-arylidendihydropyrimidine-2,4-diones **7** with a sequential process. After careful screening of the bases and conditions,[17] the best results were obtained by adding at 0 °C 1.5 equiv of potassium *tert*-butoxide to the DCM solution once the *N*-acylurea is formed (see scheme in Table 2). [18]

Thus with these results in hand, we studied the possibility to obtain the target molecules through a multi-component sequential process consisting in (1) in situ formation of the reacting carbodiimides **3** by Staudinger reaction, performed in DCM, of azides **1** and isocyanates **2**, (2) addition to the resulting solutions of acids **4** once the carbodiimide is already formed (TLC monitoring), and (3) final addition of potassium *tert*-butoxide once the *N*-acylurea intermediates are formed (TLC monitoring). The process and the results are summarized in Table 2.

Accordingly, Staudinger reaction, performed in DCM, of benzyl azide **1a** and phenyl isocyanate **2a** gave the clean formation of the corresponding carbodiimide **3c** along with Ph_3PO byproduct. Without isolating the carbodiimide, acids **1a-c** were added and the resulting *N*-acylureas cyclized by adding, in situ, potassium *tert*-butoxide, leading to the final regiospecific formation of *N*-benzyl,*N′*-phenyl-5-arylidendihydropyrimidine-2,4-diones **7a–c**, respectively, in high yields (Table 2, entries 1–3). Acid **4b** reacted smoothly also with in situ formed carbodiimides **3f,g** giving rise to the formation, after cyclization, of compounds **7d,e**, respectively, as the only regioisomers, confirming that the reaction with 'strongly asymmetric' carbodiimides is totally regioselective independently from the nature of the *N*-alkyl and *N′*-aryl substituents. Finally, the process worked smoothly also with symmetric *N,N′*-diaryl carbodiimides. Indeed, starting from phenyl azide **1d** and phenyl isocyanate **2a**, at the end of the MC process performed with acids **4b,c** we could obtain the formation of *N,N′*-diphenyl-5-arylidendihydropyrimidine-2,4-diones **7f,g** in very good overall yields (Table 1, entries 6 and 7).

In conclusion, we have developed a novel and efficient process for the synthesis of libraries of *N,N′*-disubstituted-5-arylidendihydropyrimidine-2,4-diones through a three-component sequential reaction that occurs in very mild conditions, involving simple and readily accessible starting materials. The operational simplicity and the good chemical yields, combined with favorable atom-economy aspects and a small number of synthetic steps, render this new synthetic strategy attractive and promising for the preparation of the target compounds. The application of this methodology to other Baylis–Hillman adducts and the functionalization of the C=C double bond of the final compounds are currently in progress in our laboratories and will be reported in a forthcoming full paper.

Acknowledgments

Mr. Marco Barozzi and Mr. Andrea Bassani are acknowledged for performing preliminary experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.109.

References and notes

1. For some reviews on MC reactions, see: (a) Armstrong, R. M.; Combs, A. P.; Brown, P. A.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131; (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329; (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210; (d) Dömling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318–323; (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89; (f) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, *14*, 8444–8454; (g) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472; (h) Ruijter, E.; Scheffelaar, R.; Orru, R. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234–6246.
2. Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 149–163.
3. (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499; (b) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *34*, 4101–4111.
4. Lowe, J. A., III; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johonson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielsen, J. A.; Russo, L. L.; Shirley, J. T. *J. Med. Chem.* **1991**, *34*, 624–628.
5. Shimazaki, N.; Yamazaki, H.; Yatanabe, T.; Tanaka, H. *Chem. Abstr.* **1992**, *117*, 131217.

6. Mignani, S.; Damour, D.; Doble, A.; Labaudiniere, R.; Malleron, J. L.; Plot, O.; Gueremy, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1913–1918.
7. Jones, K. A.; Weaver, D. F.; Tiedje, K. E. WO 2004009559, January 29, 2004.
8. Ishii, T.; Motoyoshi, M.; Jiyatsukesu, B. JP 63290867, November 28, 1988.
9. Wright, T. R.; Fuerst, E. P.; Ogg, A. G., Jr.; Nandihalli, U. B.; Lee, H. J. *Weed Sci.* **1995**, *43*, 47–54.
10. (a) Zee-Cheng, K.-Y.; Robins, R. K.; Cheng, C. C. *J. Org. Chem.* **1961**, *26*, 1877–1884; (b) Schlogl, K. *Monatsh. Chem.* **1958**, *89*, 61.
11. Kondo, Y.; Witkop, B. *J. Am. Chem. Soc.* **1969**, *91*, 5264–5270.
12. (a) Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2003**, *44*, 8549–8551; (b) Volonterio, A.; Ramirez de Arellano,, C.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 2161–2170; (c) Volonterio, A.; Zanda, M. *Org. Lett.* **2007**, *9*, 841–844; (d) Volonterio, A.; Zanda, M. *J. Org. Chem.* **2008**, *73*, 7486–7497; (e) Olimpieri, F.; Volonterio, A.; Zanda, M. *Synlett* **2008**, 3016–3020; (f) Olimpieri, F.; Fustero, S.; Volonterio, A.; Zanda, M. *Synthesis* **2010**, *4*, 651–660; (g) Marcelli, T.; Olimpieri, F.; Volonterio, A. *Org. Biomol. Chem.* **2011**, *9*, 5156–5161; (h) Bellucci, M. C.; Volonterio, A. *Eur. J. Org. Chem.* **2009**, 6179–6188; (i) Bellucci, M. C.; Marcelli, T.; Volonterio, A. *RSC Adv.* **2011**, *1*, 1250–1264; (j) Bellucci, M. C.; Ghilardi, A.; Volonterio, A. *Org. Biomol. Chem.* **2011**, *9*, 8379–8392; (k) Bellucci, M. C.; Volonterio, A. *Adv. Synth. Catal.* **2010**, *352*, 2791–2798; (l) Bellucci, M. C.; Volonterio, A. *Org. Chem. Insight* **2012**, *4*, 1–24.
13. For a very recent review on the Baylis–Hillman reaction, see: Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.
14. The 2-(bromomethyl)-3-aryl-2-propenoic acids could also be prepared in one step starting from the *tert*-butyl acrylate derived Baylis–Hillman adducts: Zulykama, Y.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 3892–3896.
15. A similar situation occurred also when we tried the synthesis of *N*,*N*′-dilakyl barbiturates starting from DIC or DCC with malonic acid monoesters (see Ref. 12d).
16. The regiochemistry of the two products was assessed by ^{1}H NMR: the NH signals of **6d** appears as a broad singlet, while the same NH of **6d**′ appears as a broad triplet (see Supplementary data).
17. Nucleophilic bases such as NaOH or NaOEt lead to the formation of a mixture of byproducts as well as performing the cyclization with *tert*-BuOK at higher temperatures.
18. It is worth noting that the exocyclic C=C double bond of compounds **7** could migrate to give rise the formation of the corresponding unsaturated pyrimidine structures. However, considering the NMR spectra of the final compounds, and in particular the proton chemical shift of the endocyclic methylene and the carbon chemical shifts of the C=C (see Supplementary data), this is not the case.