ORGANIC LETTERS

2003
Vol. 5, No. 25
4915−4918

Microwave-Assisted [3 + 2] Cycloadditions of Azomethine Ylides

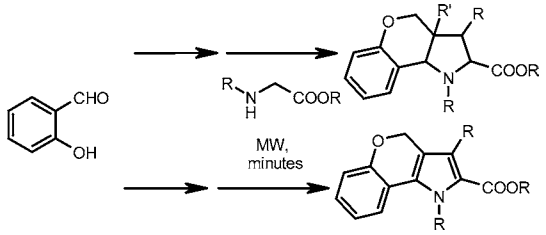
George Bashiardes,* Imad Safir, Achmet Said Mohamed, Francis Barbot, and Joelle Laduranty

Département de Chimie, Méthodologie et Synthèse de Biomolécules, SFA-UMR 6514, Université de Poitiers, 40 avenue du Recteur Pineau, 86022 Poitiers, France

george.bashiardes@univ-poitiers.fr

Received October 30, 2003

ABSTRACT



The microwave-assisted intramolecular [3 + 2] cycloaddition reaction of azomethine ylides to activated and nonactivated alkenes and alkynes is described. The procedure allows the synthesis of pyrrolidines and pyrrole products in good to excellent overall yields in short reaction times. It appears from parallel comparative studies that the microwave procedure favors the reaction times and overall purity of the crude reaction mixture. The reactions can also be performed in the absence of solvent.

The use of microwaves for carrying out reactions in the laboratory provides advantages for the synthesis of numerous types of compounds.[1−3] When the technique is applied successfully, the most evident improvements are reduced time of reaction, cleaner reactions due to fewer side-reactions, and the use of minimal quantities of solvent. Thus, microwave-assisted synthesis can be considered as more economical and environmentally friendly. We have explored the use of microwaves in the [3 + 2] cycloaddition reaction. This reaction is a useful tool for the synthesis of heterocyclic compounds when 1,3-dipolar azomethine ylides are added to alkenes or alkynes[4] to provide pyrrolidines or pyrroles efficiently from readily available starting materials. The obtained compounds can carry diverse substitution patterns by choice and, as such, could be employed as templates for screening for biological activity.[5]

In the present report, we describe the use of microwave conditions for the condensation of O-allylic and O-propargylic salicylaldehydes with α-amino esters. The cycloaddition reaction involves a polar 1,3-dipole intermediate. We therefore reasoned that, as such, the reaction should be well suited for this mode of activation. Since our objective was to explore the influence of the microwaves on the reaction as opposed to simple heating, parallel comparative reactions were performed. Each pair of reagents was treated under different conditions in order to elucidate the parameters influencing the reaction and thus determine the effect of the microwaves on the outcome of the reaction.

(1) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851−10870. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223 and references therein.

(2) Examples: Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron Lett.* **2003**, *44*, 4455−4458. Jiao, G.-S.; Castro, J. C.; Thorensen, L. H.; Burgess, K. *Org. Lett.* **2003**, *5*, 3675−3677. Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Synthesis* **2002**, 75.

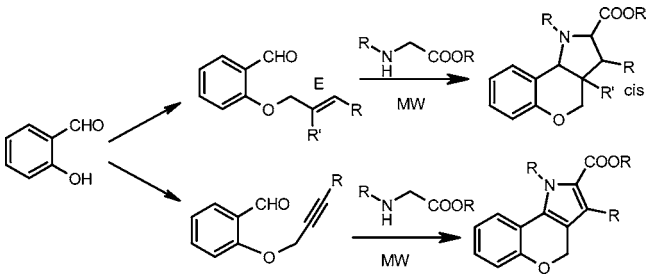
(3) De La Hoz, A.; Diaz-Ortiz A.; Langa, F. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Germany, 2003. Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452−456.

(4) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2003**, *44*, 8417−8420.

(5) Pinna, G. A.; Pirisi, M. A.; Chelucci, G.; Mussinu, J. M.; Murineddu, G.; Loriga, G.; D'Aquila, P. S.; Serra, G. *Bioorg. Med. Chem.* **2002**, *10*, 2485−2496. Bolognesi, M. L.; Andrisano, V.; Bartolini, M.; Minarini, A.; Rosini, M.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **2001**, *44*, 105−109. Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951−8955.

10.1021/ol0361195 CCC: $25.00
Published on Web 11/18/2003

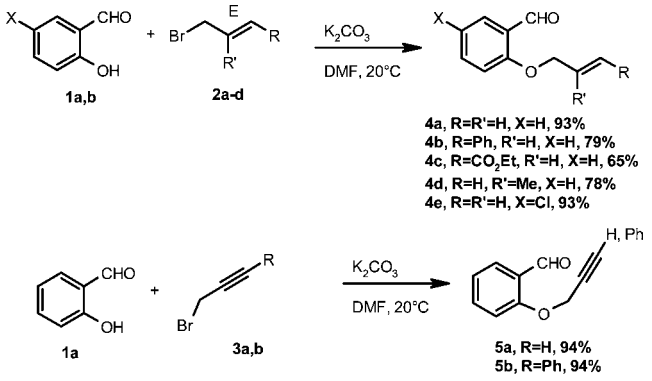
Scheme 1. Cycloadditions to Provide Pyrrolidines and Pyrroles



According to the choice of functionality, the procedure would provide final products able to be employed as diversified scaffolds for the exploration of possible biological activity.

Starting from salicylaldehyde, O-alkylation using allylic or propargylic bromides proceeds in good to excellent yields.[6] Varied starting materials were thus selected for the preparation of ω-unsaturated salicylaldehydes **4** and **5** containing diverse substitution in order to investigate the effect of functionality on the microwave-catalyzed reaction.

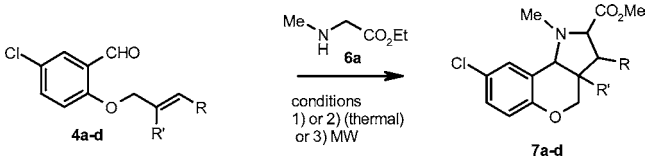
Scheme 2. *O*-Allyl and *O*-Propargylsalicylaldehydes



The condensation of compounds **4** and **5** with α-amino esters **6** was performed by three different protocols. In the first instance (conditions 1) the reactions were performed in round-bottom flasks using a Dean−Stark apparatus for the removal of the 1 equiv water that is produced in the reaction, thus calling for a minimum dilution of approximately 0.15 mol/L in the solvent (toluene).[7] Two other procedures were performed in test tubes surmounted with a condensing tube, although this latter arrangement was not obligatory. In these cases, one experiment was performed by heating the mixture in a preheated oil bath at 130 °C (conditions 2), and the other was submitted to microwave irradiation[8] (conditions 3). For the two latter procedures, if both starting materials were solids, a minimal amount of nonpolar solvent (xylene) was added if necessary to ensure thorough contact between the components. Also, identical quantities of reagents and glassware were employed. In all cases, the evolution of the reaction was monitored by thin-layer chromatography (TLC) or gas chromatography (GC) to follow the total consumption of starting aldehyde. All the products were isolated by flash column chromatography on silica gel after workup.

Condensation of the O-allylic compounds **4a**−**e** with ethyl sarcosinate **6a** proceeded to provide benzopyrano-pyrrolidines **7a**−**e** in yields ranging from 70 to 98% (Scheme 3).

Scheme 3. General Scheme for the Synthesis of Compounds **7a**−**d**[a]



[a] Conditions: (1) toluene, reflux; (2) no solvent or minimal xylene, heat in a preheated oil bath at 130 °C; (3) no solvent or minimal xylene, microwave irradiation.

The results of the above condensations are provided in Table 1. In the cases of compounds **7a**,**b**,**d**, and **e**, the all-cis[6] compounds formed in the reaction were accompanied by approximately 5% of a single diasteroisomer in which the ring junction was trans. Compound **7c** was obtained as a 1:1 mixture of diastereoisomers in which the ring junction was either cis or trans.[6]

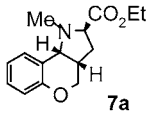
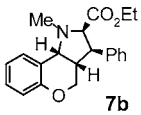
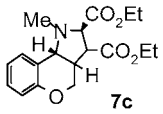
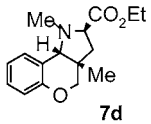
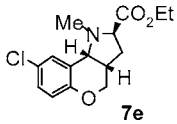
Indeed, all the reactions performed under microwaves were completed rapidly after a few minutes, except for **7d**, which was the exception. There is a clear advantage in using this mode as compared to the thermal conditions. Also, the yields under microwaves are often the highest, compared to those under thermal conditions. This reflects a cleaner reaction with fewer side-products, as observed on analysis of the crude reaction mixtures, and thus easier purification. In both cases of the activated O-allylic salicylaldehydes **4b** and **4c**, shorter reaction times were observed, the ester-substituted compound being much faster, as would be expected. Lower yields and longer reaction times were observed under thermal conditions for compound **7d**, which contains a quaternary bridgehead methyl moiety. Although longer than the other examples, the reaction times were short and greatly improved yields were achieved under microwaves. Interestingly, 5-chloro-*O*-allylsalicylaldehyde **4e**, which contains an unactivated double bond, rapidly underwent condensation with ethyl sarcosinate. Again, under microwave conditions, significant acceleration of the reaction was observed.

(6) Broggini, G.; Zecchi, G. *Synthesis* **1996**, 1280−1282.

(7) Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175−7178. Kanemasa, S.; Sakamoto, K.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1960−1968. Grigg, R.; Duffy, L. M.; Dorrity, M. J.; Malone, J. F.; Rajviroongit, S.; Thornton-Pett, M. *Tetrahedron* **1990**, *46*, 2213−2230. Harwood, L. M.; Lilley, I. A. *Tetrahedron Lett.* **1993**, *34*, 537−540.

(8) Reactions were carried out under atmospheric pressure on a CEM Discover apparatus.

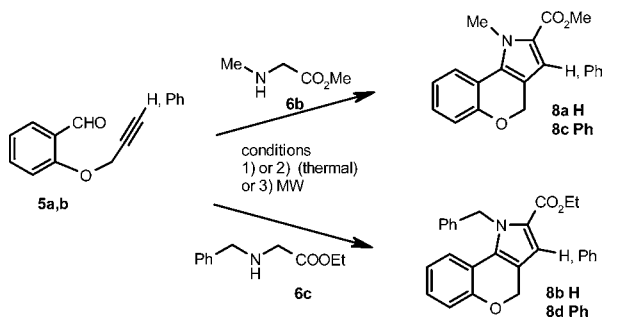
Table 1. Comparative Results for Condensation to Pyrrolidines **7**

Product[d]	Conditions 1 (thermal)[a] Duration, yield	Conditions 2 (thermal)[b] Duration, yield	Conditions 3 (MW)[b,c] Duration, yield
 **7a**	24 h, 88%	1.5 h, 92%	15 min, 93%
 **7b**	4 h, 93%	40 min, 89%	5 min, 89%
 **7c**	40 min, 81%	10 min, 93%	5 min, 98%
 **7d**	24 h, 72%	9 h, 70%	30 min, 98%
 **7e**	4 h, 90%	1 h, 76%	10 min, 81%

[a] Conditions 1: 0.15 mol/L in toluene, reflux, Dean−Stark apparatus. [b] Conditions 2 and 3 are identical in setup; they differ in the mode of heating, i.e., preheated oil bath at 130 °C or microwave irradiation. [c] Settings: 100W, 130 °C. [d] For clarity, only one enantiomer is depicted here.

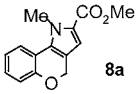
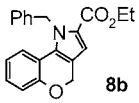
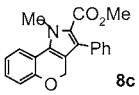
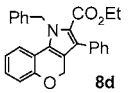
The next series of reactions that were investigated concerned the preparation of pyrrolic compounds **8a**−**d** (Scheme 4).

Scheme 4. Condensations for the Preparation of Compounds **8a**−**d**



Condensation of *ω*-propargylic benzaldehydes **5a**,**b** with methyl sarcosinate **6b** and ethyl *N*-benzylglycinate **6c**, followed by in situ oxidation either by air[9] or, more conveniently, by sulfur,[10] efficiently provides substituted benzopyrano-pyrroles **8**. Other combinations of α-amino esters and propargylic aldehydes provide further diversity.[3] The practical procedure followed for these examples involves heating the two components in order to achieve cycloaddition (consumption of starting aldehyde) followed by the in situ addition of sulfur and continued heating. As above, three comparative experiments were performed for each example (conditions 1−3). Conditions 1 and 2 involved mixing the two starting compounds and heating in a preheated oil bath at 130 °C either using a Dean−Stark apparatus (approximately 0.15 mol/L = conditions 1) or in the absence of solvent (if necessary, a minimal quantity of xylene to help mixing = conditions 2). For conditions 3, the mixture was submitted to microwave irradiation in the absence of solvent. The combined results are summarized in Table 2.

Table 2. Comparative Results for Preparation of Pyrroles **8**

Product	Conditions 1 (thermal)[a] Duration, yield	Conditions 2 (thermal)[b] Duration, yield	Conditions 3 (MW)[b,c] Duration, yield
 **8a**	2 h+2 h, 60%	0.75 h+0.5 h, 70%	10 min + 10 min, 70%
 **8b**	3 h+1 h, 78%	1 h+0.75 h, 74%	10 min + 10 min, 75%
 **8c**	2.5 h+2 h, 68%	0.75 h+0.5 h, 70%	10 min + 10 min, 74%
 **8d**	3 h+2 h, 80%	1 h+0.5 h, 78%	12 min + 10 min, 90%

[a] Conditions 1: 0.15 mol/L in toluene, reflux, Dean−Stark apparatus. [b] Conditions 2 and 3 are identical in setup; they differ in the mode of heating, i.e., preheated oil bath or microwave irradiation. [c] Settings: 100W, 130 °C.

The results indicate once more that there is a clear advantage in terms of reaction time when working under microwave conditions. The yields of isolated pyrrole compounds **8a**−**d** in this one-pot procedure are comparable, regardless of the reagents used or the experimental conditions applied. Since the completion of the experiments described in the table above, an additional procedure was explored. In this additional procedure, the aldehyde **5b**, the α-amino ester **6c**, and sulfur were all mixed in a tube with 0.5 mL of xylene and then heated under microwave irradiation for 15 min (settings 100W, 130 °C). After purification, the expected pyrrole **8d** was obtained in 90% yield.

This procedure is a new process for the one-pot multicomponent synthesis of benzopyrano-pyrroles. Indeed, work is currently underway in our laboratory to apply this procedure for the synthesis of other and simpler pyrroles by an intermolecular [3 + 2] cycloaddition.

In conclusion, we present new procedures for microwave-assisted [3 + 2] cycloadditions of azomethine ylides to

(9) Vo Quang, L.; Gaessler, H.; Vo Quang, Y. *Ang. Chem., Int. Ed. Engl.* **1981**, *20*, 880−881.

(10) Rhee, M.-H.; Vogel, Z.; Barg, J.; Bayewitch, M.; Levy, R.; Hanuš, L.; Breuer, A.; Mechoulam, R. *J. Med. Chem.* **1997**, *40*, 3228−3233.

activated or nonactivated alkenes and alkynes. The application to pyrrolidines and pyrroles is described. In all cases, the explored comparative study concluded that under microwave conditions the times of reaction are very short. The procedures described allow the efficient synthesis of diverse pyrrolidine compounds selectively, including new examples containing chiral quaternary bridgehead substituents. The process also allows the preparation of pyrroles in a one-pot multicomponent reaction. The yields are generally high to excellent, and the experimental procedures are straightforward. In most cases where one or more of the reagents employed are liquid, the reactions can be performed without solvent.

Supporting Information Available: Typical experimental procedures and selected analytical data for compounds **7b**, **7d**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0361195