ORGANIC LETTERS

2001
Vol. 3, No. 6
877−880

A Novel Multicomponent Synthesis of Polysubstituted 5-Aminooxazole and Its New Scaffold-Generating Reaction to Pyrrolo[3,4-*b*]pyridine

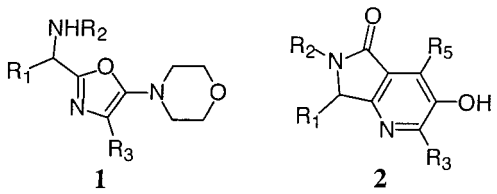
Xiaowen Sun,[†] Pierre Janvier,[†] Gang Zhao,[†] Hugues Bienaymé,[‡] and Jieping Zhu*,[†]

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France, and Rhône-Poulenc Industrialisation, 24 Av. Jean-Jaures, F-69153 Décines Cedex, France

zhu@icsn.cnrs-gif.fr

Received December 23, 2000

ABSTRACT



A novel three-component synthesis of 5-amino oxazole (1) is reported. Its subsequent reaction with α,β-unsaturated acyl chloride leads to polysubstituted pyrrolopyridine (2). A triple domino process, acylation/IMDA/retro-Michael cycloreversion, was involved in the latter process. The methodology allows the quick preparation, from simple and readily available inputs, of highly functionalized title compounds not easily accessed by other methods.

Complexity-generating/diversity-oriented high throughput synthesis of druglike compounds and libraries thereof has been a recent focus in the arsenal of combinatorial synthesis.[1,2] Being capable of combining three or more reactants together in a single ordered event, multicomponent reaction (MCR) exemplified by the Ugi 4CR offers great possibility for molecular diversity per step and is becoming a cornerstone of combinatorial syntheses.[3] Clearly, a proper union of a MCR with other reactions in a sequential or a domino process will further expand its potential.[4,5] As part of our research program directed at synthesizing druglike heterocycles, we were interested in the development of a novel multicomponent synthesis of polysubstituted 5-aminooxazole (**1**) and its subsequent use as a chemical platform to generate new scaffolds such as polysubstituted pyrrolo[3,4-*b*]pyridine (**2**). While compound **1** is known to be a useful template in designing bioactive peptides,[6] the generic structure of **2** can

[†] Institut de Chimie des Substances Naturelles.
[‡] Rhône-Poulenc Industrialisation.

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.

(2) (a) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153−6167. (b) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622−625; 625−628. (c) Sheehan, S. M.; Lalic, G.; Chen, J. S.;. Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714−2715.

(3) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647−658. (c) Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255−270. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131.

(4) Recent examples: (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1996**, *118*, 8977−8978. (b) Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. G. *Tetrahedron Lett.* **1998**, *39*, 2235−2238. (c) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647−1649. (d) Bienayme, H.; Bouzid, K. *Tetrahedron Lett.* **1999**, *40*, 2735−2738. (e) Paulvannan, K. *Tetrahedron Lett*. **1999**, *40*, 1851−1854. (f) Paulvannan, K.; Jacobs, J. W. *Tetrahedron* **1999**, *55*, 7433−7440. (g) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett*. **2000**, *2*, 709−712. (h) Hulme, C.; Ma, L.; Cherrier, M.-P.; Romano, J. J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett*. **2000**, *41*, 1883−1887.

(5) For reviews on the domino sequence, see: (a) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322. (b) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley: New York, 2000; pp 39−64. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (d) Filippini, M. H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27−76. (e) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13160.

10.1021/ol007055q CCC: $20.00
Published on Web 02/28/2001

be considered as a cyclic analogue of nicotinamide (**3**, Figure 1). Indeed, pyrrolopyridine **2** has attracted increased attention

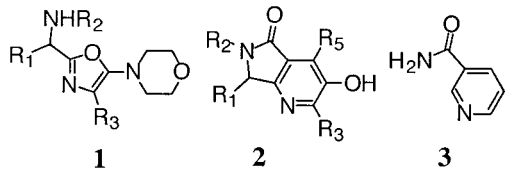
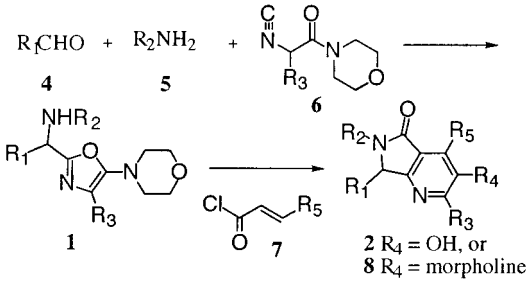


Figure 1.

as biologically active compounds such as central nervous system agents,[7] as herbicides[8] and as antidiabetic agents.[9] With a few notable exceptions,[10] most of the reported syntheses are based on the functionalization of azaphthalimide and thus are limited in scope.[11]

The reaction sequence we envisaged is highlighted in Scheme 1. A three-component reaction of an aldehyde (**4**),

Scheme 1



an amine (**5**), and a suitably functionalized isocyanoacetamide (**6**) was sought to provide a key 5-aminooxazole (**1**), which could then be used as a branching point to produce diverse bioactive chemotypes.[12] One possible new scaffold-generating reaction was illustrated by its reaction with α,β-unsaturated carboxylic acid chloride **7** to afford the pyrrolopyridine after a *directed* fragmentation.[13] A successful implementation of such a novel synthetic sequence was the purpose of the present communication.

The synthesis of oxazole has attracted renewed interest as a result of its presence in a number of bioactive marine natural products.[14] However, none of the existing methods could satisfy our general goal aimed at using oxazole as a scaffold-generating template in a diversity-oriented synthetic program. Consequently, an expeditious construction of oxazole via a multicomponent reaction was sought. After some experimentation, it was found that simply heating a methanol solution of an aldehyde (**4**), an amine (**5**), and an isocyanoacetamide (**6**) led to the formation of 5-amino oxazole (**1**) in good yield.[15] From three aldehyde inputs, eight amine inputs, and two isonitrile inputs, some representative oxazoles were synthesized (Figure 2.)[16] The condensation was performed with approximately equimolar quantities of the three components, thus simplifying the purification step. Under these mild conditions, ring-chain tautomerization of isonitrile **6** to 2-unsubstituted oxazole via a nitrilium intermediate was not observed,[17] nor was the Pictet−Spengler reaction even when (3,4-dimethoxy)phenethylamine **5a** containing a properly positioned electron-rich aromatic ring was employed.[18] With a secondary amine as input, a yield of pure oxazole greater than 90% was obtained (**1g** and **1h**). As expected for the Ugi-type reaction, racemic oxazoles were obtained when enantiomerically pure isonitriles **6** (R = Bn or phenyl) were used as inputs. On the other hand, when proline methyl ester was used as the amine input, a moderate asymmetric induction was observed that led to two separable diastereomers in a ratio of 2.5/1 (**1h**). To the best of our knowledge, this procedure represents the first multicomponent synthesis of 2,4,5-trisubstituted oxazole.[19]

In contrast to 5-alkoxyoxazole,[20] studies on the cycloaddition of the 5-amino derivative are relatively rare.[21,22] Kondrat'eva et al. have shown that the intermolecular reaction of the latter with dienophile was quite sensitive to the reaction conditions leading to [2 + 4], [2 + 3], and even

(6) (a) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217−3222. (b) Von Geldern, T. W.; Kester, J. A.; Bal, R.; Wu-Wong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 957−967; 968−981.

(7) Anzini, M.; Cappelli, A.; Vomero, S.; Giorgi, G.; Langer, T.; Bruni, G.; Romeo, M. R.; Basile, A. S. *J. Med. Chem.* **1996**, *39*, 4275−4284.

(8) Duerr, D.; Brunner, H. G.; Szczepanski, H. U.S. Patent US4721522, 1988; *Chem. Abstr.* **1988**, *109*, 170430b.

(9) Hitzel, V.; Geisen, K.; Werner, R.; Guenter, R. Ger. Offen. 2948522, 1981; *Chem. Abstr.* **1981**, *95*, 150632h.

(10) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1031−1032. (b) Campbell, J. B.; Firor, J. W. *J. Org. Chem.* **1995**, *60*, 5243−5249. (c) Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951−1960.

(11) (a) Goto, T.; Saito, M.; Sato, R. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4178−4180. (b) Hitchings, G. J.; Vernon, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 623−624. (c) Hitchings, G. J.; Vernon, J. M. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1757−1763. (d) Goto, T.; Utsunomiya, S.; Aiba, H.; Hayasaka, H.; Endo, M.; Watanabe, R.; Ishizaki, T.; Sato, R.; Saito, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1901−1910.

(12) For a brief discussion, see: Bienaymé, H.; Hulme, C.; Oddon, G.; Schmidtt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329.

(13) For the concept of "from libraries to libraries", see: Ostresh, J. M.; Husar, G. M.; Blondelle, S. E.; Dörner, B.; Weber, P. A.; Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138−11142.

(14) For recent syntheses: (a) Cardwell, K. S.; Hermitage, S. A.; Sjolin, A. *Tetrahedron Lett.* **2000**, *41*, 4239−4242. (b) Nishida, A.; Fuwa, M.; Naruto, S.; Sugano, Y.; Saito, H.; Nakagawa, M. *Tetrahedron Lett.* **2000**, *41*, 4791−4794. (c) Lee, J. C.; Song, I.-G. *Tetrahedron Lett.* **2000**, *41*, 5891−5894. (d) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469−471. (e) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555−557. (f) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165−1168.

(15) For syntheses of 5-amino oxazole, see: (a) Ferris, J. P.; Orgel, L. E. *J. Am. Chem. Soc.* **1966**, *88*, 3829−3831. (b) Martin, A. R.; Ketcham, R. *J. Org. Chem.* **1966**, *31*, 3612−3615. (c) Sekiya, M.; Suzuki, J. *Chem. Pharm. Bull.* **1970**, *18*, 2242−2246. (d) Clerin, D.; Kille, G.; Fleury, J. P. *Tetrahedron* **1974**, *30*, 469−474. (e) Chupp, J. P.; Leschinsky, K. L. *J. Heterocycl. Chem.* **1980**, *17*, 711−715. (f) Freeman, F.; Kim, D. S. H. L. *Tetrahedron Lett.* **1989**, *30*, 2631−2632. (g) Bossio, R.; Marcaccini, S.; Pepino, R.; Polo, C.; Torroba, T. *Heterocycles* **1989**, *29*, 1829−1833. (h) Zhou, X.-T.; Lin, Y.-R.; Dai, L.-X.; Sun, J. *Tetrahedron* **1998**, *54*, 12445−12456.

(16) The purity of the raw material was not measured carefully for the individual reaction. From the ^{1}H NMR spectra of the crude reaction mixture, the purity of **1g** and **1h** exceeded 75%.

(17) Chupp, J. P.; Leschinsky, K. L. *J. Heterocycl. Chem.* **1980**, 705−709.

(18) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.

(19) For a two-step synthesis via a key 3C Passerini reaction, see: Bossio, R.; Marcaccini, S.; Pepino, R. *Liebigs Ann. Chem.* **1991**, 1107−1108.

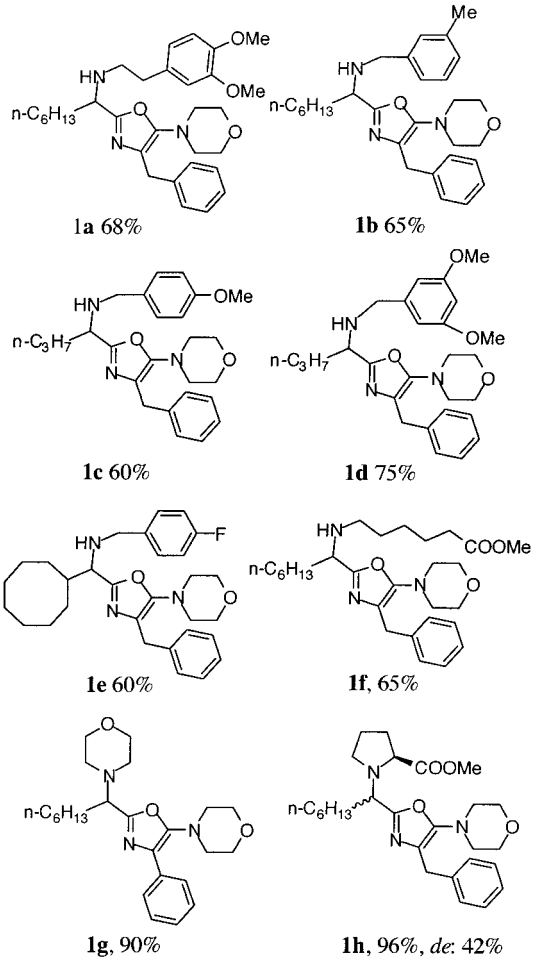


Figure 2. Isolated yield of analytically pure compound.

[2 + 2] cycloadducts. To channel these different reactivities into a productive process, we set out to examine the previously unexplored intramolecular cycloaddition of 5-aminooxazole.[23] The presence of the secondary amine in compounds **1** provided an ideal handle for realization of this endeavor. Heating a solution of oxazole **1a** and acid chloride

(20) Reviews: (a) Hassner, A.; Fischer, B. *Heterocycles* **1993**, *35*, 1441−1465. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389−437. (c) Lakhan, R.; Ternai, B. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1974; Vol. 17, pp 99−211.

(21) (a) Kondrat'eva, G. Y.; Aitzhanova, M. A.; Bogdanov, V. S. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1976**, 2146−2147; *Chem. Abstr.* **1977**, *86*, 121223j. (b) Kondrat'eva, G. Y.; Aitzhanova, M. A.; Bogdanov, V. S.; Chizhov, O. S. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1979**, 1313−1322; *Chem. Abstr* **1979**, *91*, 140753b. (c) Bogdanov, V. S.; Kondrat'eva, G. Y.; Aitzhanova, M. A. *Izv. Akad. Nauk. SSSR Ser. Khim.* **1980**, 1017−1029; *Chem. Abstr.* **1980**, *93*, 185242s.

(22) (a) McEwen, W. E.; Grossi, A. V.; MacDonald, R. J.; Stamegna, A. P. *J. Org. Chem.* **1980**, *45*, 1301−1308. (b) Shimada, S. *J. Heterocycl. Chem.* **1987**, *24*, 1237−1241.

(23) For related examples, see: (a) Levin, J. L.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325−4332. (b) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327−8329. (c) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580−5585. (d) Levin, J. I. *Tetrahedron Lett.* **1989**, *30*, 2355−2358. (e) Jung, M. E.; Dansereau, S. M. K. *Heterocycles* **1994**, *39*, 767−778. (f) Vedejs, E.; Piotrowski, D. W.; Tuci, F. C. *J. Org. Chem.* **2000**, *65*, 5498−5505. (g) Padaw, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233−3235 and references therein.

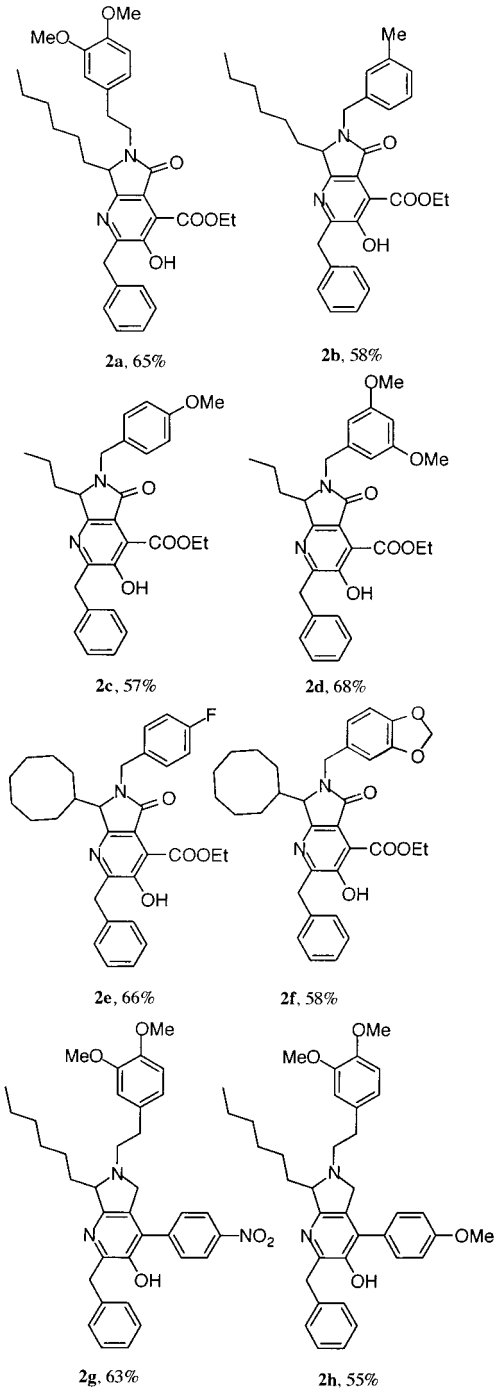
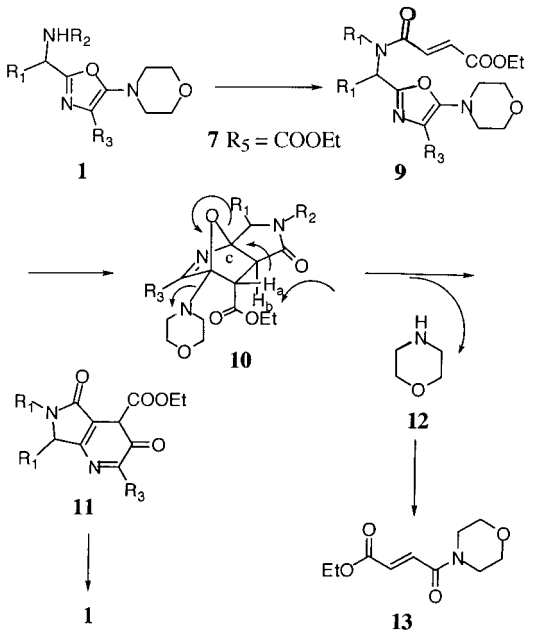


Figure 3. Isolated yield of analytically pure compound.

7a (R_5 = COOEt) in toluene at reflux temperature led to the formation of pyrrolopyridine **2a** in 65% yield (Figure 3). Toluene was the solvent of choice as the same reaction performed in other solvents such as THF, MeCN, and benzene produced only low yields of the desired pyrrolopyridine. Other acyl chlorides, such as *p*-nitro cinnamic acid chloride **7b** (R_5 = 4-NO_2-C_6H_5) and *p*-methoxy cinnamic acid chloride **7c** (R_5 = 4-OMe-C_6H_5) can also be used as dienophiles.

Scheme 2



A possible reaction scenario is shown in Scheme 2. Thus, acylation of secondary amine of oxazole **1** gave the amide **9**, which underwent intramolecular Diels−Alder reaction affording the bridged tricyclic intermediate (**10**). Base-catalyzed retro-Michael cycloreversion then furnished the pyrrolopyridine. The following facts are in accord with this reaction sequence: (1) In sharp contrast to Kondrat'eva's reports,[20] reaction between oxazole **1a** and *N*-phenylmaleimide did not give the corresponding cycloadduct, probably because of the steric hindrance of oxazole **1a**. This result supports the idea that acylation preceded cycloaddition.[24] (2) When the reaction was carried out in CH_2Cl_2 at room temperature, we were able to isolate the intermediate **10** (R_1 = *n*-C_6H_{13}, R_2 = 2-(3,4-dimethoxyphenyl) ethyl, R_3 = Bn). The coupling constant between H_a and H_b (J_{Ha-Hb} = 4.1 Hz) indicated a gauche relationship (dihedral angle of 40° or so) between these two protons. For the inherent ring strain imposed by the connecting bridge, only the lactam-*exo*-ester *endo* mode of cycloaddition was possible, leading to observed compound **10**. In this intermediate, the proton H_b is properly aligned with the C_c−O bond, which facilitates the difficult 5-*endo*-*trig* reversal leading to **11** and morpholine **12**, the latter being isolated as its corresponding amide **13**.[25] Thus for conformational reasons, this retro-Michael cycloreversion dominated over the alternative fragmentation assisted by the lone pair electron on the morpholine nitrogen (compound **8**, Scheme 1), an otherwise normal process.[20−22]

In conclusion, we report a novel multicomponent synthesis of polysubstituted 5-aminooxazole starting from simple and readily available inputs. Its subsequent reaction with α,β-unsaturated acyl chloride led to polyfunctionalized pyrrolopyridine. The latter one-pot reaction involves a triple domino sequence: acylation/IMDA/retro-Michael cycloreversion. The chemistry described is especially suitable for combinatorial synthesis since the oxazole and the bicyclic skeleton of pyrrolopyridine can be "decorated" by different substituents at will. The methodology developed should be easily adapted to solid-phase synthesis as well as automation.

Acknowledgment. Financial support from Rhône-Poulenc Industralisation (X.W.S. and G.Z.), Rhodia (P.J.) ,and CNRS is gratefully acknowledged. This paper is dedicated with deep respect to Dr. R. Beugelmans

Supporting Information Available: Physical data for compounds **1a**−**h**, **2a**−**h**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL007055Q

(24) Cyclic olefins are generally more reactive as dienophiles than their acyclic counterparts in a given Diels−Alder reaction; see: (a) Vaughan, W. R.; Anderson, K. S. *J. Org. Chem.* **1956**, *21*, 673−683. (b) Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962**, 615−618.

(25) Keay, B. A.; Rajapaksy, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093−1098.