ORGANIC LETTERS

2009
Vol. 11, No. 8
1817−1820

Concise Synthesis of Tricyclic Isoindolinones via One-Pot Cascade Multicomponent Sequences

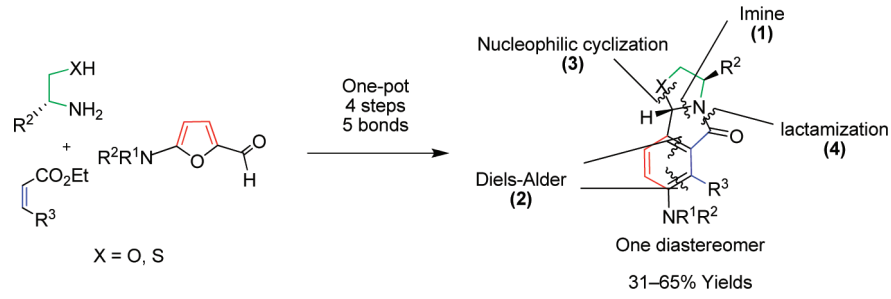
Raouf Medimagh,[†] Sylvain Marque,*[,†] Damien Prim,*[,†] Jérôme Marrot,[†] and Saber Chatti[‡]

Institut Lavoisier de Versailles (ILV) UMR CNRS 8180, Université de Versailles-Saint-Quentin-en-Yvelines, 45 Avenue des Etats-Unis, 78 035 Versailles, Cedex, France, and Laboratoire de Chimie Verte, Institut National de Recherche et d'Analyse Physico-chimique (INRAP), Pôle Technologique de Sidi Thabet, 2020 Sidi Thabet, Tunisia

prim@chimie.uvsq.fr; sylvain.marque@chimie.uvsq.fr

Received February 25, 2009

ABSTRACT



A series of enantiopure tricyclic isoindolinones has been successfully synthesized through a one-pot selective cascade process from furan derivatives. The synthesis is straightforward and gave good overall yields taking into account the concomitant formation of five C−C, C−O, and C−N bonds. The strategy was extended to the preparation of a thiazolidine analogue.

Rapid synthesis of complex molecules in a single operation without isolation of intermediates is one of the current concerns of the scientific community[1] that drives increasing efforts. Recently, cascade multicomponent reactions (CMCR) have emerged as powerful and bond-forming efficient tools that allow the preparation of polycyclic targets by connecting several components in a one-pot sequential and efficient manner.[2] Due to their high versatility,[3] small heterocycles were particularly attractive in CMCR. In this context, we became interested in the preparation of potentially biological active enantiopure tricyclic lactam−isoindolinone derivatives[4] (Scheme 1). Traditionally, the synthesis of such targets (X = O), recently rationalized by Allin et al.,[5] was realized using 2-formylbenzoic acid and amino alcohols through the formation of bonds (d) and (e). We anticipated that the carboxylic group, essential to the formation of the lactam

[†] Université de Versailles-Saint-Quentin-en-Yvelines.
[‡] Institut National de Recherche et d'Analyse Physico-chimique (INRAP).

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Chapman, C. J.; Frost, C. *Synthesis* **2007**, 1.

(2) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Tietze, L. F.; Evers, T. H.; Töpken, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 903. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (d) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321.

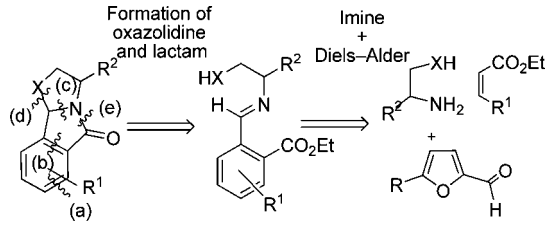
(3) (a) Constantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Isambert, N.; Lavilla, R. *Chem.—Eur. J.* **2008**, *14*, 8444.

(4) For selected examples, see: (a) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95. (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905. (c) Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron* **2005**, *61*, 1335.

(5) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627.

10.1021/ol9003965 CCC: $40.75
Published on Web 03/25/2009

Scheme 1. Access to Tricyclic Isoindolinones from 5-Amino-2-furaldehydes

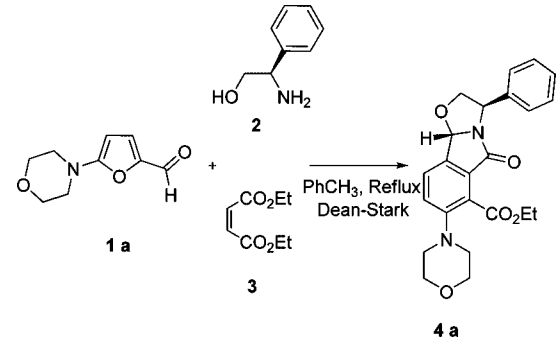


moiety, could be installed at the aromatic ring through a Diels−Alder reaction involving furan derivatives as the diene- and carboxylic ester-substituted activated dienophiles. This strategy would provide an expedient and straightforward access to tricyclic isoindolinones starting from easily available activated furaldehydes. We have contributed to this area by addressing the reactivity of activated 5-amino-2-furaldehydes[6] in one-pot, two-step sequences.[7] The latter afforded polysubstituted aromatics or oxabicyclic structures by in situ trapping of versatile aminofuraldehydes intermediates. An intriguing question was whether we would be able to selectively create five concomitant bonds (a)−(e) to successively form the aromatic ring, the imine−oxazolidine moiety, and the isoindolinone heterocycle by ring-closing lactamization (Scheme 1). An additional and critical point was the diastereoselective formation of the oxazolidine ring step under rather hard Diels−Alder conditions and in the presence of electrophiles such as carbethoxy groups.

Based on previous studies devoted to Diels−Alder reactions,[7,8] we have been exploring the possibility of achieving the one-pot three component four-steps preparation of enantiopure tricyclic isoindolinones.

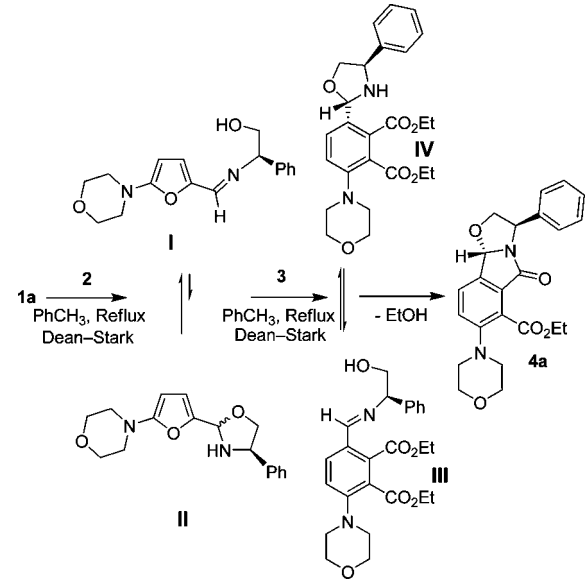
Initial Diels−Alder reactions involving 5-amino-2-furaldehydes with 3 equiv of diethyl maleate were unsuccessful.[8] In fact, an increase of the reactivity of the diene was required to allow [4 + 2] cycloadditions using diethyl maleate as the dienophile. In this context, cycloadducts could be recently obtained using 5-amino-2-furanmethanols, arising from the reduction of the parent carboxaldehyde moiety, as the diene. Moreover, previous comparisons between furaldehyde derivatives and their corresponding hydrazones as potential dienes pointed to the enhanced reactivity of the latter.[9] Based on these findings, we anticipated that the early formation of a furylimine would allow a further cycloaddition to take place. Indeed, the reaction of 5-amino-2-furaldehyde **1a** with diethyl maleate in the presence of phenylglycinol was monitored by ^{1}H NMR and evidenced the formation of a transient furylimine species at an early stage of the process. Interestingly, we were able to observe the progressive decrease of characteristic signal of the furylimine species. Careful observation of ^{1}H NMR spectra of crude material clearly indicated the disappearance of the starting furan protons as well as those of furylimine and the presence of cycloadduct characteristic signals. This seminal result paved the way to selective sequential cascades involving the early and in situ formation of an amino furylimine species, which then may undergo Diels−Alder cycloaddition with diethyl maleate. Gratifyingly, optimization of the reaction conditions,[7,8] reactant ratios, as well as media concentration allowed the determination of the optimal **1**/amino alcohol **2**/dienophile **3** ratio as 1:1:2. Under Dean−Stark conditions in refluxing toluene (Scheme 2), the target molecules were obtained in high conversion and yield.

Scheme 2. One-Pot Access to Tricyclic Isoindolinone **4a**



The selective access to tricyclic lactams **4a** deserves some comments (Scheme 3). Condensation of an α-amino alcohol with an aldehyde is known to give a mixture of the expected hydroxy imine such as **I** and the corresponding ring-closed

Scheme 3. Evolution of Possible Intermediates



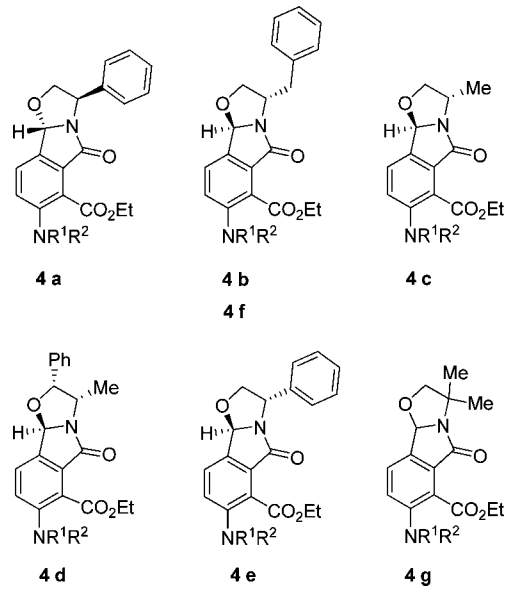
(6) (a) Prim, D.; Kirsch, G. *Tetrahedron* **1999**, *55*, 6511. (b) Prim, D.; Kirsch, G.; Nicoud, J. F. *Synlett* **1998**, 383. (c) Migianu, E.; Prim, D.; Kirsch, G. *Synlett* **2000**, 459.

(7) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S.; Zarrouk, H. *J. Org. Chem.* **2008**, *73*, 2191.

(8) Medimagh, R.; Marque, S.; Prim, D.; Chatti, S. *Heterocycles* **2009**, *78*, 679.

(9) Potts, K. T.; Walsh, E. B. *J. Org. Chem.* **1988**, *53*, 1199.

Table 1. Tricyclic Isoindolinones from Various Amino Alcohols



compd	NR^1R^2	yield (%)[a]	amino alcohol	$[\alpha]_D$[b] (deg)
4a	R^1, R^2 = morpholinyl	40	(*R*)-phenylglycinol	−98
4b	R^1, R^2 = morpholinyl	65	(*S*)-phenylalaninol	−12
4c	R^1, R^2 = morpholinyl	35	(*S*)-alaninol	−5
4d	R^1, R^2 = morpholinyl	45	(-)-norephedrine	+16
4e	R^1 = Me, R^2 = 4-anisidinyl	34	(*S*)-phenylglycinol	+93
4f	R^1 = Me, R^2 = allyl	33	(*S*)-phenylalaninol	−169
4g	R^1, R^2 = morpholinyl	35	2-amino-2-methylpropanol	

[a] Isolated yields. [b] Calculated in CH_2Cl_2, see the experimental procedures for concentration details.

oxazolidine **II**.[10] Monitoring the reaction by ^{1}H NMR clearly evidenced that the hydroxy imine species **I** was the early and predominant intermediate produced (singlet 7.9 ppm) in full agreement with literature data.[11] The transient hydroxy imine **I** underwent cycloaddition leading to the intermediate **III**, which may equilibrate with **IV**.

In the last step, ring closure with concomitant loss of ethanol cleanly produced the target lactam **4a**. ^{1}H NMR spectra of the crude did not reveal the presence of side products. Although both intermediates **III** and **IV** existed in solution, lactamization process most likely occurred from oxazolidine **IV**, according to literature data.[5]

Careful examination of ^{1}H NMR spectra of the crude material confirmed the presence of only one of the possible diastereomers. As observed in the case of oxazolidines arising from aromatic aldehydes bearing electron-withdrawing groups,[5,12] the selective cyclization process from **III** is assumed to afford the more favored trans isomer **IV**.

Relative configuration of C18−C15 has been determined both by single-crystal X-ray analysis[13] and by NOE experiments (Figure 1). The absolute configuration was assigned on the basis of the fixed stereocenter of the starting amino alcohol.

The one-pot sequence was then extended to several amino alcohols in combination with variously substituted 5-amino-2-furaldehydes (cyclic, aromatic, and allylic amino subtituents), affording **4b**−**g** in fair to good yields ranging from 33 to 65% yields in four steps (Table 1).

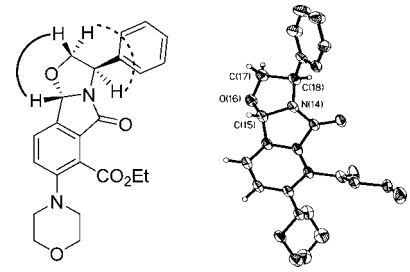


Figure 1. ORTEP X-ray plot and NOE for **4a**.

For all these cases, only one diastereomer was selectively obtained during the oxazolidine ring construction, even under rather harsh reaction conditions.

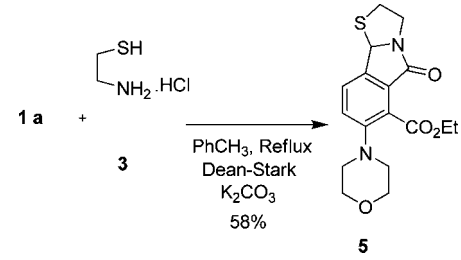
Interestingly, the use of amino alcohol bearing an additional chiral center such as norephedrine affected neither the isolated yield nor the selective chirality transfert process

(10) Allin, S. M.; Hodkinson, C. C.; Taj, N. *Synlett* **1996**, 781.
(11) Scialdone, M. A.; Meyers, A. I. *Terahedron Lett.* **1994**, *35*, 7533.
(12) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537.

(see **4d**). It is worth noting that increase of substitution at the amino alcohol, when using 2-amino-2-methylpropanol, only poorly affected conversion and yields, **4g** being obtained in 35% yield.

We next examined the use of amino thiol instead of amino alcohol, in order to prepare the corresponding thiazolidine **5** (Scheme 4). Attempts to use aminoethanethiol hydrochloride without neutralization failed. In fact, neutralization of the latter prior to the reaction sequence was not required, and the presence of an additional base in the media such as K_2CO_3 (1 equiv) was successful, allowing a selective preparation of **5** in 58% yield.

Scheme 4. Synthesis of Tricyclic Thiazolidine **5**



Among the classic tools to measure the reaction efficiency, alternative ones, such as "greenness",[14] have begun to emerge. In this context, solvent-free reactions that induce benefits such as cost savings, decreased energy consumption, and reduced reaction times become an appealing alternative to enhance this factor.[15] With this in mind, we decided to test the feasibility of our sequence under solvent-free conditions. Reacting the components in aforementioned proportions in a sealed tube at 115 °C afforded the desired product **4a** in 24 h in 41% yield (Table 2). It is worthy to note that reaction time could be significantly reduced without loss of yield or stereoselectivity.

Table 2. Solvent-Free Obtention of **4a**

conditions			
solvent	time (h)	T (°C)	yield (%) (four steps)
toluene	96	Dean−Stark	40
solvent free	24	115	41

In summary, we succeeded in the efficient preparation of enantiopure tricyclic isoindolinones via a novel one-pot, three-component cascade process. This unprecedented selective sequence involved the formation of a transient imine followed by Diels−Alder cycloaddition, oxazolidine ring closure, and lactamization reactions. The formation of five concomitant C−C, C−O, and C−N bonds, under appealing solvent-free conditions, fulfills not only current organic chemistry concerns but also green chemistry principles. In addition, this methodology could be extended to the formation of thiazolidine analogues by using amino thiols instead of amino alcohols.

Acknowledgment. We are very grateful to the Université de Versailles-Saint-Quentin-en-Yvelines for material support and to CNRS for financial support, especially for a grant (R.M.) and ANR program (ANR-07-CP2D-14-01).

Supporting Information Available: Experimental procedure and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9003965

(13) Crystal data: $C_{23}H_{24}N_2O_5$, $M_w = 408.44$, orthorhombic, space group $P2_12_12_1$; dimensions: $a = 8.7153(7)$ Å, $b = 9.8625(9)$ Å, $c = 24.055(2)$ Å, $V = 2067.7(3)$ Å^3; $Z = 4$; $\mu = 1.312$ mm^{-1}; 36210 reflections measured at 100 K; independent reflections: 3404 [2497 $F_o > 4\sigma(F_o)$]; data were collected up to a $2\theta_{max}$ value of 60.10° (99.2% coverage). Number of variables: 297; $R_1 = 0.0399$, w$R_2 = 0.1060$, $S = 1.072$; highest residual electron density 0.214 e Å^{-3} (all data $R_1 = 0.0702$, w$R_2 = 0.1295$). CCDC 717782.

(14) Walsh, P. J.; Li, H.; Anaya de Parrodi, C. *Chem. Rev.* **2007**, *107*, 2503.

(15) (a) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159. (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.