ORGANIC LETTERS

2011
Vol. 13, No. 19
5120–5123

Base-Catalyzed Povarov Reaction: An Unusual [1,3] Sigmatropic Rearrangement to Dihydropyrimidobenzimidazoles

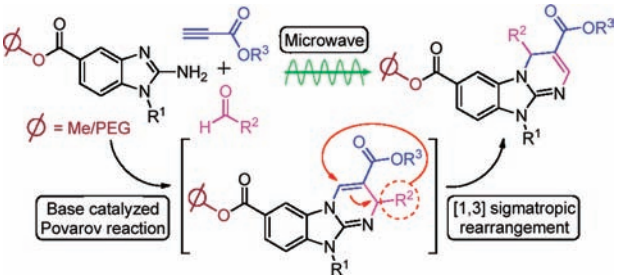
Chih-Hau Chen, Gorakh S. Yellol, Po-Tsung Lin, and Chung-Ming Sun*

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan

cmsun@mail.nctu.edu.tw

Received July 23, 2011

ABSTRACT

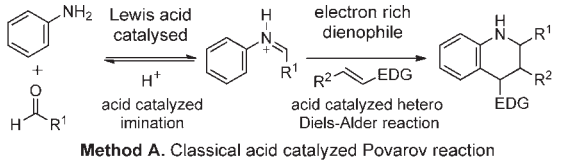


A novel base-catalyzed Povarov reaction of arylamines, aldehydes, and electron-deficient dienophiles has been developed. An unprecedented in situ [1,3] sigmatropic rearrangement leading to 4,10-dihydropyrimido[1,2-*a*]benzimidazoles has also been discovered. An insight of the plausible mechanism is discussed and supported by X-ray crystal study. This cascade reaction is achieved in a one-pot multicomponent fashion on soluble support under microwave conditions.

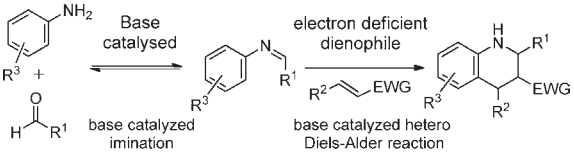
Hetero-Diels–Alder cycloaddition is recognized as a powerful reaction in the synthetic strategies of natural and unnatural polyheterocycles owing to its rich synthetic diversity.[1] Since the pioneering works of Povarov, acid-mediated [4 + 2] hetero-Diels–Alder cycloaddition between the C=C–N=C azadiene moieties of *N*-arylimines and dienophiles has become an established route to various heterocycles.[2] However, despite being an attractive strategy, its application is limited to condensation of an amine with an aldehyde and final cyclization between *N*-arylimines and electron-rich dienophiles, which is usually catalyzed by acids[3] (method A, Scheme 1). A careful literature survey revealed that the Povarov reaction has never been explored under basic conditions and even not applied to electron-deficient dienophiles. This encouraged us to investigate a base-catalyzed Povarov reaction as well as with electron-deficient dienophiles (method B).

The ubiquity of polyheterocyclic systems in biomedically relevant molecules and natural products has stimu-

Scheme 1. Classical Povarov Reaction and Our Strategy



Method A. Classical acid catalyzed Povarov reaction



Method B. Our strategy of base catalyzed Povarov reaction

(1) (a) Desrat, S.; van de Weghe, P. *J. Org. Chem.* **2009**, *74*, 6728. (b) Gaddam, V.; Nagarajan, R. *Org. Lett.* **2008**, *10*, 1975. (c) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250.

(2) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656.

(3) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.

(4) Fischer, J., Ganellin, C. R., Eds. *Analogue-Based Drug Discovery*; Wiley-VCH: Weinheim, 2002.

(5) (a) Kaan, H. Y. K.; Ulaganathan, V.; Rath, O.; Prokopcová, H.; Dallinger, D.; Kappe, C. O.; Kozielski, F. *J. Med. Chem.* **2010**, *53*, 5676. (b) Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutus, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem.* **1990**, *33*, 1510.

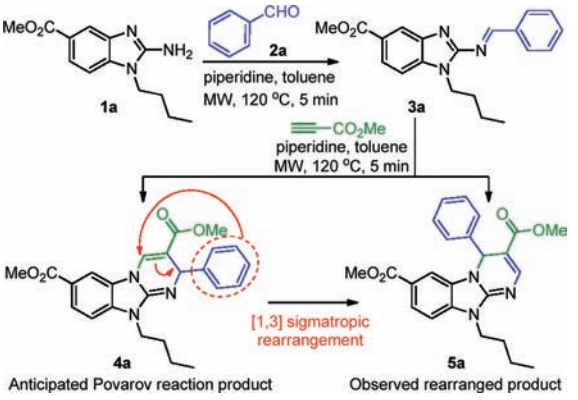
10.1021/ol201985p
Published on Web 09/02/2011

lated many efforts for their synthesis.[4] The design concept of the presently synthesized target has originated from the recognition of the biological role of the dihydropyrimidines and benzimidazoles which exhibits a wide range of pharmacological properties[5] including nociceptin/orphanin FQ receptor agonism[6] and HIV-1 integrase inhibition.[7] Thus, the generation of a fused heterocyclic skeleton resembling druglike molecules has a substantial intellectual appeal and thus provoked us to synthesize benzimidazolyl-fused dihydropyrimidines.

Modern synergetic approaches integrating the soluble polymer-supported synthesis with microwave synthesis provides a powerful strategy to generate a diversified molecular library to speed up initial drug discovery.[8] Microwave heating greatly accelerates the rate of reactions, while polymer support facilitates purifications by a simple precipitation technique.[9] Our laboratory is fascinated by the application of such eco-friendly technologies to develop rapid synthetic methods for biologically promising molecules.[10] In continuation of our studies, here we disclose an unprecedented base-catalyzed Povarov reaction of heteroarylimines with electron-deficient dienophiles and subsequent unusual [1,3] sigmatropic rearrangement and the development of a multicomponent strategy toward the soluble support for synthesis of the dihydropyrimido[1,2-*a*]benzimidazole library.

The most promising method to investigate the Povarov reaction under basic conditions is to synthesize the arylimine first and then treat it with various dienophiles. At the outset of our studies, the viability of the imination was first attempted by a reaction of 2-aminobenzimidazole **1a** with benzaldehyde **2a** (optimization table provided in the Supporting Information). The desired imine formation was not observed under thermal reflux conditions in toluene, using trifluoroacetic acid in dichloromethane and utilizing scandium triflate as a Lewis acid catalyst in methanol, chloroform, and toluene under reflux as well as microwave conditions. However, use of the ammonium chloride in toluene under thermal and microwave conditions affords imine in moderate yields. Our investigation of the intended base-catalyzed Povarov reaction led us to investigate piperidine as a catalyst for imine preparation. The use of piperidine (0.5 equiv) in toluene under microwave conditions was found to provide the best results. Mechanistically, condensation of aldehyde with piperidine provides the piperidinium hydroxide salt.[11] The nucleophilic

Scheme 2. Base-Catalyzed Povarov Reaction and Rearrangement



addition of benzimidazol-2-amine **1a** to piperidinium hydroxide salt with expulsion of water and a piperidine unit affords benzimidazole-2-imine derivative **3a**.

To investigate the Povarov reaction under basic conditions, as a model reaction, it was decided to use methyl propiolate as reactive dienophile and piperidine as a base catalyst. Consequently, benzimidazole-2-imine **3a** was treated with methyl propiolate and piperidine in toluene under microwave conditions at 120 °C. After 5 min, benzimidazole-fused dihydropyrimidine was obtained as a product, whose structure was considered as **4a** according to the anticipated results (Scheme 2).

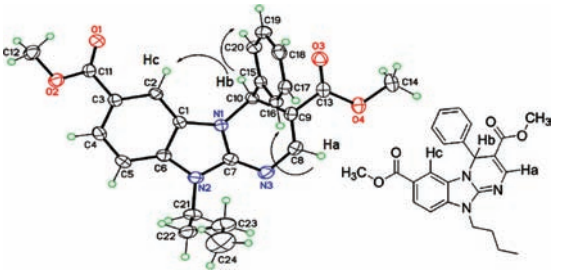


Figure 1. ORTEP diagram and key NOE enhancements of **5a**.

In addition to spectroscopic studies, additional 1D NOE studies were carried out for the confirmation of structure and regioselectivity of the resulting tricyclic heterocycle. Peculiarly, the results of 1D NOE experiments did not correspond to the structure of proposed Povarov reaction product **4a**. The irradiation of proton Ha in fused tricyclic heterocycle enhances the signals of phenyl protons by 2.10%. However, the irradiation of Hb proton enhanced the signals of phenyl proton by 4.79% as well as shows enhancement of Hc proton by 2.90% (Figure 1). These observations indicate that the phenyl group could be in proximity of the Hb proton rather than the expected Ha proton. With this ambiguity, the structure of the fused

(6) Hayashi, S.; Hirao, A.; Imai, A.; Nakamura, H.; Murata, Y.; Ohashi, K.; Nakata, E. *J. Med. Chem.* **2009**, *52*, 610.

(7) Jones, E. D.; Vandegraaff, N.; Le, G.; Choi, N.; Issa, W.; Macfarlane, K.; Thienthong, N.; Winfield, L. J.; Coates, J. A. V.; Lu, L.; Li, X.; Feng, X.; Yu, C.; Rhodes, D. I.; Deadman, J. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5913.

(8) Hsiao, Y. S.; Yellol, G. S.; Chen, L. H.; Sun, C. M. *J. Comb. Chem.* **2010**, *12*, 723.

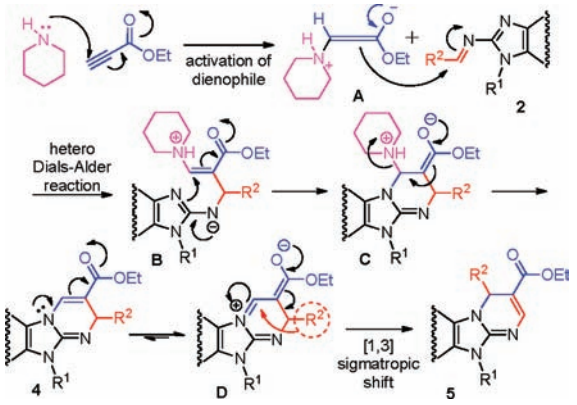
(9) (a) Zhang, W. *Chem. Rev.* **2009**, *109*, 749. (b) Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2009**, *11*, 5706.

(10) (a) Chen, C. H.; Kuo, J.; Yellol, G. S.; Sun, C. M. *Chem. Asian J.* **2011**, *6*, 1557. (b) Yellol, G. S.; Chung, T. W.; Sun, C. M. *Chem. Commun.* **2010**, *46*, 9170. (c) Lai, J. J.; Salunke, D. B.; Sun, C. M. *Org. Lett.* **2010**, *12*, 2174.

(11) Correa, W. H.; Edwards, J. K.; McCluskey, A.; McKinnon, I.; Scott, J. L. *Green Chem.* **2003**, *5*, 30.

triheterocyclic product was further analyzed by an X-ray crystallographic study. Surprisingly, the X-ray crystallographic data revealed that the product structure is **5a** rather than expected **4a**. The ORTEP diagram of compound **5a** is depicted in Figure 1 (crystallographic data in the Supporting Information). The phenyl group is linked to the C10 carbon rather than the expected C8 carbon atom. The results of 1D NOE experiments absolutely match the structure **5a**. This combined study clearly indicates the rearrangement of Povarov reaction product **4a** to dihydropyrimidobenzimidazole **5a**. The phenyl group was migrated from the C8 carbon to the C10 carbon through electronic rearrangement in the dihydropyrimidine ring system. This is the first report of this kind of unusual [1,3] sigmatropic rearrangement.

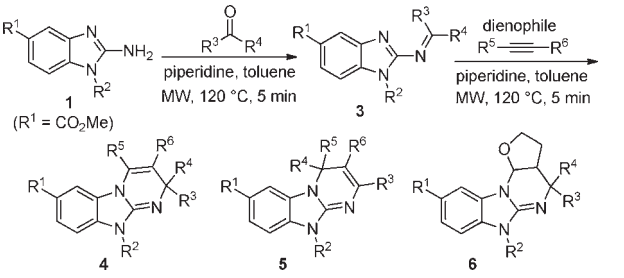
Scheme 3. Plausible Mechanism for Base-Catalyzed Povarov Reaction and [1,3] Sigmatropic Rearrangement

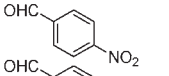
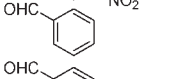
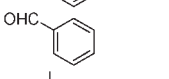
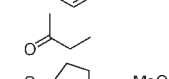
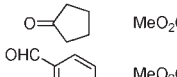
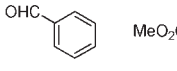


Plausible steps involved in the base-catalyzed Povarov reaction and in situ [1,3] sigmatropic rearrangement are depicted in Scheme 3. Initially, electron-deficient dienophile would activate through the base. Piperidine reacts with ethyl propiolate to form reactive allene adduct **A**, which spontaneously reacts with imine **2** to afford the adduct **B**. The subsequent cyclization by 1,4-Mannich-type addition delivers ionic intermediate **C**. Expulsion of the piperidine molecule from adduct **C** furnished Povarov reaction product **4**. The mechanism of the further [1,3] sigmatropic rearrangement of **4** was envisioned through a series of electronic revolvement for the formation of more stable conjugate system **5**. The electronic rearrangement could be initialized through lone pairs of benzimidazolyl nitrogen of **4** to form the ionic intermediate **D**. Finally, the [1,3] sigmatropic transfer of aryl or alkyl group could triggered by the electron transfer on the acrylate to form a fully conjugated stable system through stabilization of the ionic intermediate to furnish dihydropyrimido[1,2-*a*]benzimidazole **5**.

Having achieved inspiring results for the base-catalyzed regioselective Povarov reaction and in situ sigmatropic rearrangement in a model reaction, we explored its scope and limitations with various aldehydes and dienophiles (Table 1). The reaction of 2-aminobenzimidazoles **1** with

Table 1. Exploring Povarov Reaction–Rearrangement Strategy[a]



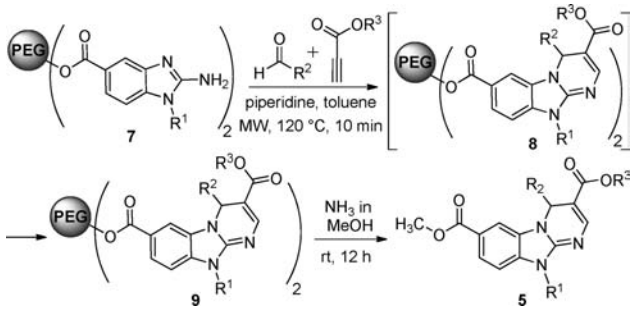
entry	R^2	R^3 R^4	dienophile R^5—≡—R^6	product 4 / 5 / 6	yield (%)[b]
1			—≡—CO_2Me	**5b**	71
2			—≡—CO_2Et	**5c**	91
3				**6a**[c]	61
4			—≡—CO_2Me	**4a**	39
5			MeO_2C—≡—CO_2Me	**4b**	43
6			MeO_2C—≡—CO_2Me	**4c**	63

[a] Only representative examples are shown in this table. All examples are included in the Supporting Information. [b] Yields of the isolated product. [c] Reactions carried out in sealed tube.

various aldehydes **2** smoothly afforded the corresponding imines **3** with good yields over 5 min under microwave irradiation. While ketones required harsh conditions (the reaction was carried out with sodium hydride for 10 min) to deliver the corresponding imine as compared to aldehydes. The generality of the Povarov cascade reaction was further investigated with different dienophiles. The electron-withdrawing monosubstituted alkynes reacted smoothly to furnish the corresponding rearranged triheterocyclic product **5** (entries 1–2). Electron-donating dienophiles were also investigated under the base-catalyzed Povarov cascade reaction. Benzo[*d*]imidazole-2-imine **3** was treated with 2,3-dihydrofuran under basic conditions (reaction carried out in a sealed tube for 24 h) to produce Povarov product **6** regioselectively. The subsequent rearrangement was not observed due to unsuitable electronic requirements and the rigid nature of the Povarov reaction product (entry 3). To the best of our knowledge, this is the first report of the synthesis of this novel tetra-heterocyclic scaffold **6**. Ketones instead of aldehydes were also examined in the Povarov cascade reaction, which furnished the corresponding Povarov reaction product **4** (entries 4 and 5). However, the [1,3] sigmatropic shift of the alkyl or aryl group was not observed with ketones and disubstituted alkyne dienophiles because both its electron-withdrawing groups stabilize the Povarov reaction product through conjugation. Remarkably, the sequential process worked

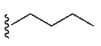
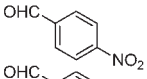
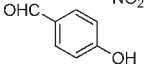
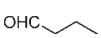
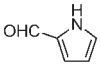
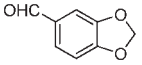
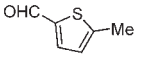
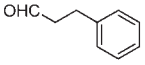
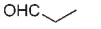
well with a broad range of aldehydes and dienophiles to give the corresponding products in good yields with high regioselectivity.

Scheme 4. PEG-Supported Multicomponent Povarov Reaction



With successful exploration of stepwise imine formation and a Povarov reaction followed by a [1,3] sigmatropic rearrangement reaction under basic conditions, we next focused our attention on a one-pot multicomponent reaction of heteroarylamine, aldehydes, and dienophiles to produce dihydropyrimidine−benzimidazole. Unfortunately, various attempts to achieve the multicomponent reaction are unsuccessful at providing the desired product. On the basis of previous experience, it was contemplated that the synergetic effect of microwave irradiation and PEG support may offer an opportunity to access the Povarov reaction in a multicomponent fashion. Accordingly, PEG-immobilized 2-aminobenzimidazole **7** was prepared through a four-step synthetic procedure with built-in diversity (R^1).[8] To investigate the multicomponent reaction, PEG-linked 2-aminobenzimidazole **7** was treated with aldehyde, alkyne, and piperidine in toluene at 120 °C under microwave irradiation. Gratifyingly, polymer-supported dihydropyrimido[1,2-*a*]benzimidazole **9** was obtained in 10 min through a multicomponent Povarov reaction and in situ [1,3] sigmatropic rearrangement (Scheme 4). The acceleration of the multicomponent Povarov reaction kinetics could be interpreted by the fact that the polyethylene glycol support provided a microwave absorption environment which could efficiently conduct the microwave energy to the reactants. PEG-bound compound **9** was purified by precipitation and washing with cold ether to remove excess reagents and by-product. Finally, polymer support was cleaved in the methanolic solution of ammonia to furnish 4,10-dihydropyrimido-[1,2-*a*]benzimidazoles **5** in good yields. Table 2 shows representative examples to demonstrate the feasibility of this novel multicomponent cascade reaction to provide dihydropyrimidobenzimidazole analogues with manifold appendages. In sharp contrast to conventional Povarov reaction which involves acid-catalyzed reaction of aromatic aldehydes and electron-rich dienophiles, we have demonstrated the piperidine-catalyzed Povarov protocol can be applied to electron-deficient acetylenes as well as a variety of aldehydes including aliphatic aldehydes and ketones. The synergetic effect of microwave irradiation and PEG support greatly accelerate the reaction in multicomponent fashion. Additionally, the PEG support allows the progress of the reaction to be easily monitored by regular proton NMR. It furthermore obviates the need for purification along the way since the excess reagents are removed in the precipitation process.

Table 2. Scope of Povarov Multicomponet Reaction[a]

entry	R^1	R^2CHO	$H-\equiv-R^3$	purity (%)[b]	yield (%)[c]
5d			$H-\equiv-CO_2Et$	82	88
5e			$H-\equiv-CO_2Et$	72	68
5f			$H-\equiv-CO_2Me$	89	73
5g			$H-\equiv-CO_2Et$	74	77
5h			$H-\equiv-CO_2Me$	73	71
5i			$H-\equiv-CO_2Et$	93	89
5j			$H-\equiv-CO_2Me$	96	86
5k			$H-\equiv-CO_2Me$	78	79

[a] Only representative examples are shown in this table. A library of the 21 compounds is included in the Supporting Information. [b] HPLC purity. [c] Yields were determined on the weight of purified samples.

In summary, we have successfully achieved four goals that comprise (i) a base-catalyzed Povarov reaction of heteroaryl amines, aldehydes, and alkynes; (ii) utilization of electron-deficient dienophiles in a Povarov reaction; (iii) discovery of an unprecedented [1,3] sigmatropic rearrangement; and (iv) a soluble polymer-supported short route by one-pot Povarov multicomponent reaction under microwave conditions. The strategy provides an efficient chemical pathway to access dihydropyrimido[1,2-*a*]-benzimidazoles in high yields with excellent regioselectivity that is compatible with a wide range of substrates. The extension of this method with different arylamines, carbonyl components, and dienophiles will certainly provide ample opportunities for the synthesis of a wide range of relevant compounds with potential biological interest.

Acknowledgment. We thank the National Science Council of Taiwan for financial assistance.

Supporting Information Available. Full experimental details and copies of ^1H and ^{13}C NMR, mass, and IR spectra for **4**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.