JOC Article

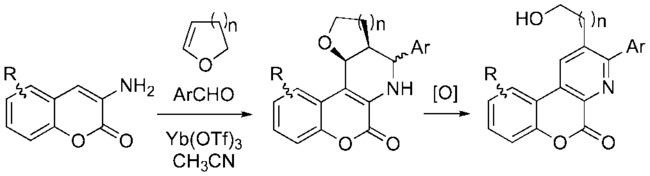
Povarov Reactions Involving 3-Aminocoumarins: Synthesis of 1,2,3,4-Tetrahydropyrido[2,3-*c*]coumarins and Pyrido[2,3-*c*]coumarins

Amit A. Kudale,[†] Jamie Kendall,[†] David O. Miller,[‡] Julie L. Collins,[‡] and
Graham J. Bodwell*[,†]

Department of Chemistry, Memorial University, St. John's, NL, Canada A1B 3X7, and CREAIT Network,
Memorial University, St. John's, NL, Canada A1C 5S7

gbodwell@mun.ca

Received July 21, 2008



Condensation of 3-aminocoumarin (**5**) with 4-nitrobenzaldehyde (**8**) afforded a 2-azadiene (**9**), which reacted with various electron-rich alkenes (10 examples) in the presence of Yb(OTf)$_3$ to afford 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins. Yields were generally good, but the diastereomeric ratios were highly variable. The products arose through a formal [4 + 2] cycloaddition (inverse electron demand Diels−Alder reaction) followed by tautomerization. As such, these are examples of the Povarov reaction. A range of 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins was then synthesized using a three-component version of this reaction, which involves in situ formation of the 2-azadiene component. Some of these products were converted into the corresponding pyrido[2,3-*c*]coumarins upon treatment with various oxidants, the most effective of which proved to be nitrous gases.

Introduction

Multicomponent reactions (MCRs) continue to attract attention as they can result in a substantial increase in molecular complexity and provide opportunities for high levels of convergence in synthesis.[1] The use of MCRs has therefore been frequently adopted by the pharmaceutical industry for the development of combinatorial libraries and the identification of lead compounds.[2] MCRs have also been utilized in the total synthesis of natural products.[3]

The inherent reactivity of carbonyl compounds with amines is often exploited in the development of MCRs.[4] The one-pot version of the Povarov reaction is such an example. In its original form, however, the Povarov reaction was not an MCR. Povarov initially described the participation of aldimines derived from aniline and aromatic aldehydes in a formal [4 + 2] cycloaddition with electron-rich alkenes (rendering it a formal inverse electron demand Diels−Alder reaction) in the presence of a Lewis acid catalyst and the subsequent tautomerization of the initial adduct to give 1,2,3,4-tetrahydroquinoline derivatives (eq 1, Scheme 1).[5] It was only much later that this reaction was developed into a one-pot operation (MCR), in which the aldimine was generated in situ.[6] In fact, this development triggered an ongoing period of considerable interest in the

---

[†] Department of Chemistry.

[‡] CREAIT Network.

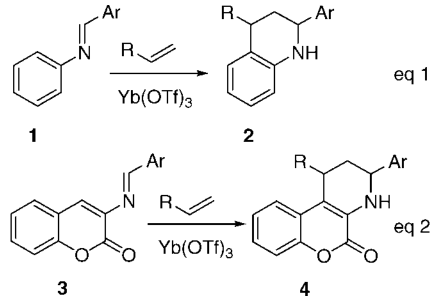
(1) For review articles on multicomponent reactions see: (a) Tejedor, D.; Garcia-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484–491. (b) Zhu, J.; Bienaymé, H. In *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. (c) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471–1499. (d) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329. (e) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (f) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472. (g) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.

(2) (a) Blackwell, H. E. *Curr. Opin. Chem. Biol.* **2006**, *10*, 203–212. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Bräuer, S.; Almstetter, M.; Antuch, W.; Behnke, D.; Taube, R.; Furer, P.; Hess, S. *J. Comb. Chem.* **2005**, *7*, 218–226. (d) Shoda, M.; Harada, T.; Kogami, Y.; Tsujita, R.; Akashi, H.; Kouji, H.; Stahure, F. L.; Xue, L.; Bajorath, J. *J. Med. Chem.* **2004**, *47*, 4286–4290. (e) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53–66. (f) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (g) Dömling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318–323.

(3) For example: (a) (±)-Preethulia coumarin. Appendino, G.; Cravotto, G.; Minassi, A.; Palmisano, G. *Eur. J. Org. Chem.* **2001**, 3711–3717. (b) Eurystatin A: Schmidt, U.; Weinbrenner, S. *J. Chem. Soc., Chem. Commun.* **1994**, *100*, 3–1004. (c) (±)-Magnoshinin. Yoshida, S.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *Synlett* **1994**, 895–898. (d) (−)-Decarbamoylsaxitoxin. Yong, C.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001–7006. (e) (+)-Furanomycin. Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510.

10.1021/jo801411p CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/27/2008

SCHEME 1. Povarov Reaction

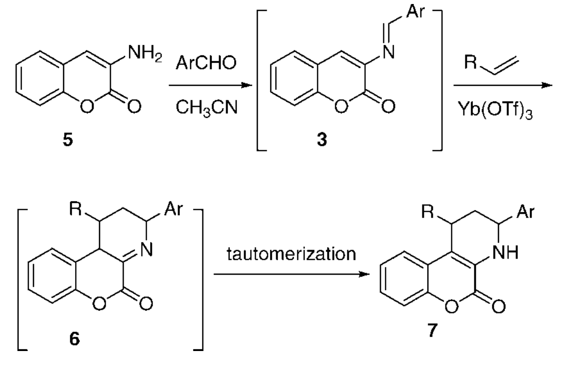


Povarov reaction,[7] which followed nearly three decades of relative obscurity since Povarov's original report.[8]

An important finding in the mid 1990s was that various lanthanide metal salts catalyze the one-pot Povarov reaction.[6] More recently, a variety of cost-effective and environment-friendly catalysts have been reported by Perumal[7a−g] and others.[7i−n] In general, aliphatic aldehydes have been found to be poor participants for this type of chemistry. However, Batey and Menéndez have independently shown that aliphatic aldehydes or aldehyde equivalents can be employed under appropriate conditions (slow addition of the aldehyde or aldehyde equivalent to the aniline and dienophile in the presence of a mild Lewis acid).[9] This reaction has also been carried out in the absence of a Lewis acid catalyst by using fluorous solvents.[10] The Povarov reaction has also found applications in total synthesis, such as in the synthesis of (±)-martinelline, (±)-martinellic acid, luotonin A, and camptothecin.[11] Nevertheless, it has so far been limited almost exclusively to the synthesis of tetrahydroquinolines because, with very few exceptions,[12] only anilines have been used successfully as the amine component. The application of amines other than anilines, if successful, would provide a direct route to a variety of heterocycles, which are uncommon or otherwise not easily accessible.

During the course of our efforts aimed at the development of new families of electron-deficient dienes for application in the inverse electron demand Diels−Alder (IEDDA) reaction,[13] we identified coumarin-fused, electron-deficient 2-azadienes as reasonable candidates for reaction with electron-rich alkenes. In fact, the IEDDA reaction of this class of dienes, which should be accessible from the condensation of 3-aminocoumarin with an aldehyde, coincides with the original form of the Povarov reaction. 3-Aminocoumarin has been known for close to a century, but there are very few reports of imines derived from this system.[14] There are no previous reports of such imines being used as dienes in the IEDDA (or Povarov) reaction. The 2-pyrone ring of the coumarin system is partially aromatic.[15] As such, 3-aminocoumarins behave like enamines in some cases (e.g., hydrolysis under acidic aqueous conditions)[16] and like anilines in others (e.g., Fischer indole synthesis).[17] We thus envisioned that 3-aminocoumarin would readily form an aldimine upon reaction with an aldehyde and then take part in a Povarov reaction in the presence of an electron-rich alkene and a suitable Lewis acid catalyst. The partial aromatic character of the pyrone unit would also be expected to favor the tautomerization of the initial cycloadduct (Scheme 2).

SCHEME 2. Povarov Reaction Involving 3-Aminocoumarin



Results and Discussion

For the initial study of the proposed IEDDA reactions, the coumarin-fused 2-azadiene **9** was prepared by the condensation of 3-aminocoumarin (**5**)[18] and 4-nitrobenzaldehyde (**8**) using modified Bishnoi conditions (Scheme 3).[19] Based on our previous experience[13] of using enamines as electron-rich dienophiles in the IEDDA reaction, the enamine derived from

---

(4) For example: (a) Elders, N.; Schmitz, R. F.; Kanter, F.; Ruijter, E.; Groen, M. B.; Orru, R. *J. Org. Chem.* **2007**, *72*, 6135–6142. (b) Yang, B.-L.; Tian, S.-K. *Eur. J. Org. Chem.* **2007**, 4646–4650. (c) El Kaïm, L.; Gizolme, M.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 4169–4180. (d) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465–2468. (e) Allegretti, M.; Berdini, V.; Cesta, C.; Curti, R.; Nicolini, L.; Topai, A. *Tetrahedron Lett.* **2001**, *42*, 4257–4259. (f) Jönsson, D.; Molin, H.; Undén, A. *Tetrahedron Lett.* **1998**, *39*, 1059–1062. (g) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734–742. (h) Ugi, I. *Angew. Chem., Int. Ed.* **1961**, 18–21. (i) Robinson, R. *J. Chem. Soc.* **1917**, 762–768.

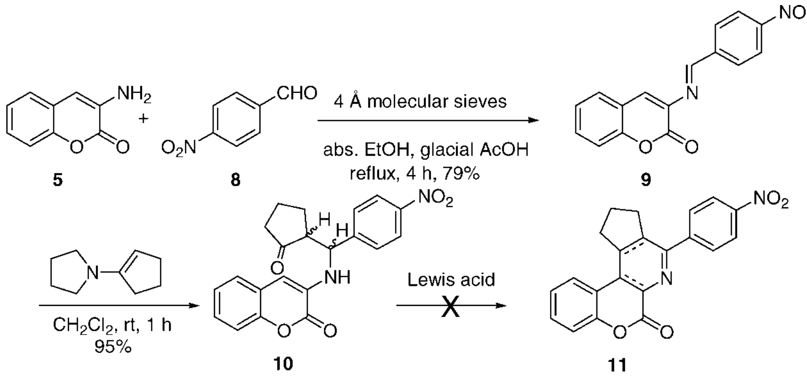
(5) (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670. (b) Povarov, L. S.; Grigos, V. I.; Makhailov, B. M. *Izv. Akad. Nauk. SSSR* **1963**, 2039–2041. (c) Povarov, L. S.; Makhailov, B. M. *Izv. Akad. Nauk. SSSR* **1963**, 955–956.

(6) (a) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462–6467. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545–546. (c) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288. (d) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195–1202. (e) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fuziwara, Y. *Synthesis* **1995**, 801–804. (f) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423–424. (g) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233–234.

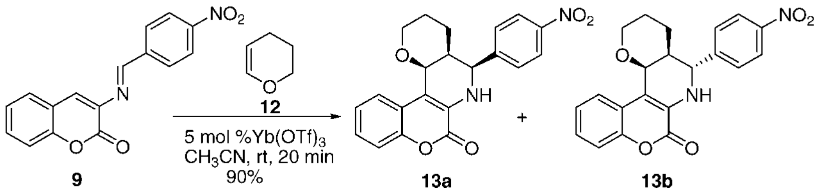
(7) For representative publications, see: (a) Sridharan, V.; Perumal, P. T.; Avendaño, C.; Menéndez, J. C. *Org. Biomol. Chem.* **2007**, *5*, 1351–1353. (b) Savitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 3589–3593. (c) Arumugam, P.; Perumal, P. T. *Chem. Lett.* **2006**, *35*, 632–633. (d) Elamparuthi, E.; Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *ARKIVOC* **2005**, 6–16. (e) Kumar, R. S.; Nagarajan, R.; Perumal, P. T. *Synthesis* **2004**, 949–959. (f) Nagarajan, R.; Mangesh, C. J.; Perumal, P. T. *Synthesis* **2004**, 69–74. (g) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2003**, *44*, 3653–3657. (h) Nagarajan, R.; Chitra, S.; Perumal, P. T. *Tetrahedron* **2001**, *57*, 3419–3423. (i) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 673–681. (j) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Madhuri, C. R.; Sabitha, G. *Synlett* **2001**, 1065–1068. (k) Yadav, J. S.; Subba Reddy, B. V.; Srinivas, R.; Madhuri, C.; Ramalingam, T. *Synlett* **2001**, 240–242. (l) Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Reddy, P. S. R. *Tetrahedron Lett.* **2002**, *43*, 3853–3856. (m) Maiti, G.; Kundu, P. *Tetrahedron Lett.* **2006**, *47*, 5733–5736. (n) Xia, M.; Lu, Y. *Synlett* **2005**, 2357–2361. (o) Li, Y.; Zhang, J.; Dong, L.; Yan, M. *Chin. J. Chem.* **2006**, *24*, 929–932. (p) Manian, R.; Jayashankaran, J.; Ramesh, R.; Ragunathan, R. *Tetrahedron Lett.* **2006**, *47*, 7571–7574. (q) Han, B.; Jia, X.-D.; Jin, X.-L.; Zhou, Y.-L.; Yang, L.; Liu, Z.-L.; Yu, W. *Tetrahedron Lett.* **2006**, *47*, 3545–3547. (r) Zhou, Y.; Xiaodong, J.; Rui, L.; Zhengang, L.; Zhongli, L.; Longmin, W. *Tetrahedron Lett.* **2005**, *46*, 8937–8939. (s) Zhou, Y.-L.; Jia, X.-D.; Li, R.; Han, B.; Wu, L.-M. *Chin. J. Chem.* **2007**, *25*, 422–425. (t) Gaddam, V.; Nagarajan, R. *Tetrahedron Lett.* **2007**, *48*, 7335–7338. (u) Manina, R.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 4139–4142. (v) Reddy, S. M.; Srinivasulu, M.; Reddy, T. S.; Narsimhulu, M.; Venkateswarlu, Y. *Indian J. Heterocycl. Chem.* **2007**, *16*, 315–316. (w) Kouznetsov, V. V.; Cruz, U. M.; Zubkov, F. I.; Nikitina, E. V. *Synthesis* **2007**, 375–384. (x) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Synthesis* **2008**, 1039–1044. Also see ref 5.

(8) (a) Laschat, S.; Noe, R.; Riedel, M. *Organometallics* **1993**, *12*, 3738–3742. (b) Lucchini, V.; Prato, M.; Scorrano, G.; Stivanello, M.; Valle, G. *J. Chem. Soc. Perkin Trans. 2* **1992**, 259–266. (c) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855–5858. (d) Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P. *J. Org. Chem.* **1988**, *53*, 2251–2258. (e) Worth, D. F.; Elslager, E. F.; Perricone, S. C. *J. Heterocycl. Chem.* **1974**, *11*, 69–70.

SCHEME 3. Reaction between an Enamine and Coumarin-Fused 2-Azadiene 9



SCHEME 4. Povarov Reaction between Diene 9 and DHP (12)



cyclopentanone and pyrrolidine was reacted with 2-azadiene **9** at room temperature for 1 h. Disappointingly, an inseparable mixture of diastereomeric products **10** arising from 1,2-addition to the imine was obtained (95% yield). Several attempts to cyclize these products to the desired cyclic/aromatized systems under Lewis acid catalysis failed (Scheme 3).[20]

The use of cyclic vinyl ethers, another commonly used class of electron-rich dienophiles in the IEDDA reaction, was then investigated. Accordingly, 3,4-dihydro-2*H*-pyran (DHP, 3.0 equiv) was allowed to react with diene **9** in the presence of 5 mol % Yb(OTf)$_3$ (Scheme 4). Gratifyingly, a 36:64 mixture of diastereomeric products arising from the anticipated Povarov reaction was isolated in 90% combined yield.[21] The two diastereomers were formally the products of *endo* and *exo* addition in an IEDDA reaction followed by tautomerization of the initial cycloadduct. No other product was isolated from this reaction. The relative stereochemistry was determined using standard 1D and 2D NMR techniques. Although the retention of the relative stereochemistry of the dienophile in both adducts is entirely consistent with a concerted mechanism, a stepwise mechanism cannot be ruled out.[22] If a stepwise mechanism is operating, the ring closure must occur in a highly diastereoselective fashion.

A series of other dienophiles were reacted with diene **9** under similar reaction conditions (Table 1). Reactions were initially run at room temperature, and those that showed no signs of progress after several hours were heated at reflux. With the exception of ethyl vinyl ether (entry 5, 25%), the yields were generally good (61−90%). However, the *endo*/*exo* ratios, which (like **13a,b**) were determined by ^{1}H NMR analysis of the crude reaction mixtures, did not appear to follow any clear trend. Selectivities ranged from >95:5 (entries 6, 8, 10) to 8:92 (entry 7). As expected, the reaction proceeded more rapidly as the dienophile became more electron-rich. Vinyl ethers (entries 1, 2, 5) reacted faster than phenyl vinyl sulfide (entry 4) and *N*-vinylpyrrolidinone (entry 3). The rates of reactions of the styrene derivatives (entries 7−9) were influenced significantly by the nature of the substituent at the 4-position (Br < H < OMe),[23] which is consistent with the development of significant positive charge at the benzylic position of the dienophile at the transition state. This would be expected for both an asynchronus concerted mechanism and a stepwise mechanism.

Having established thatcoumarin-fused 2-azadiene **9** participates in the Povarov reaction with various electron-rich dienophiles, the possibility of developing this reaction into

---

(9) (a) Powell, D. A.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 7569–7573. Also see refs 7k and 10b.

(10) (a) Legros, J.; Crousse, B.; Ourevitch, M.; Bonnet-Delpon, D. *Synlett* **2006**, 1899–1902. (b) Spanedda, M. V.; Hoang, V. D.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2003**, *44*, 217–219.

(11) (a) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913–4916. (b) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. Also see: (c) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362–2363. (d) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977–3984.

(12) Povarov, L. S. *Chem. Heterocycl. Compd. (N. Y.)* **1979**, 1694–1695.

(13) (a) Dang, A.-T.; Miller, D. O.; Dawe, L. N.; Bodwell, G. J. *Org. Lett.* **2008**, *10*, 233–236. (b) Bodwell, G. J.; Hawco, K. M.; Satou, T. *Synlett* **2003**, 879–881. (c) Bodwell, G. J.; Hawco, K. M.; da Silva, R. P. *Synlett* **2003**, 179–182. (d) Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, 477–479. (e) Bodwell, G. J.; Pi, Z. *Tetrahedron Lett.* **1997**, *38*, 309–312.

(14) (a) Kulkarni, Y. D.; Srivastava, D.; Bishnoi, A.; Dua, P. R. *J. Indian Chem. Soc.* **1996**, *73*, 173–175. (b) Tripathy, P. K.; Mukerjee, A. K. *Indian J. Chem.* **1987**, *26B*, 61–62. (c) Kumar, P.; Mukerjee, A. K. *Indian J. Chem.* **1980**, *19B*, 704–707. (d) Linch, F. W. *J. Chem. Soc.* **1912**, *101*, 1759–1765. (e) Linch, F. W. *J. Chem. Soc.* **1912**, *101*, 1755–1759.

(15) Osborne, A. G.; Cremlyn, R. J.; Warmsley, J. F. *Spectrochim. Acta, Part A* **1995**, *51*, 2525–2530.

(16) (a) Trivedi, K.; Sethna, S. *J. Org. Chem.* **1960**, *25*, 1817–1819. (b) Chakravarti, D.; Dutta, S. P.; Mitra, A. K. *Curr. Sci.* **1965**, 177.

(17) Khan, M. A.; Lucia, M. *Bol. Soc. Quim. Peru* **1979**, *45*, 42–45.

(18) Kudale, A. A.; Kendall, J.; Warford, C. C.; Wilkins, N. D.; Bodwell, G. J. *Tetrahedron Lett.* **2007**, *48*, 5077–5080.

(19) 4 Å molecular sieves were added to the reaction mixture, and the rest of the procedure was same as reported by Bishnoi; see ref 14e.

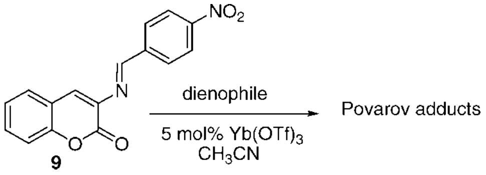
(20) The use of 10 mol % AlCl$_3$, BiCl$_3$, and Yb(OTf)$_3$ resulted in no reaction at either room temperature or reflux in tetralin.

(21) The diastereomeric ratio was determined from ^{1}H NMR analysis of crude reaction mixture.

(22) For some discussions on concerted and stepwise mechanisms of Diels−Alder reactions, see: (a) Bongini, A.; Panunzio, M. *Eur. J. Org. Chem.* **2006**, 972–977. (b) Mayr, H.; Ofial, A. R.; Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013–2020. (c) Chen, J. S.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 12303–12309.

(23) At room temperature, the reaction with 4-bromostyrene showed no signs of progress after 4 h. So, it was then heated at reflux.

TABLE 1. **Povarov Reactions Between Azadiene 9 and Various Electron-Rich Dienophiles**



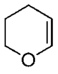
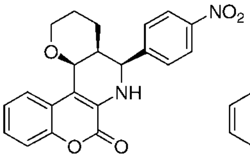
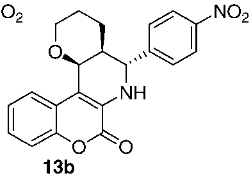
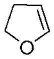
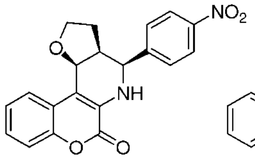
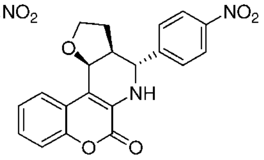
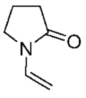
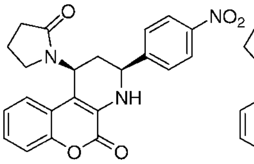
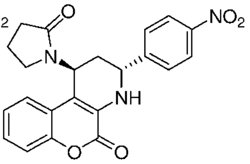
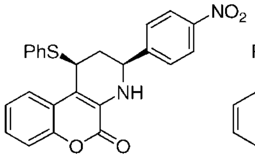
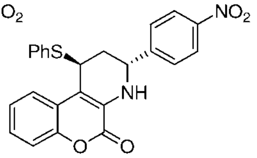
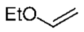
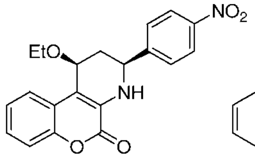
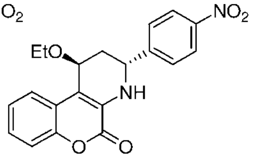
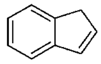
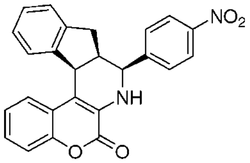
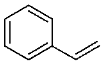
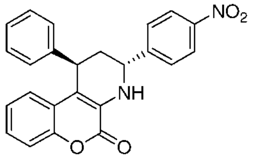
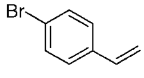
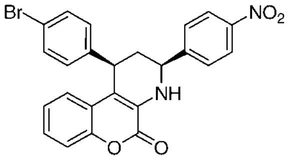
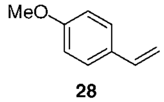
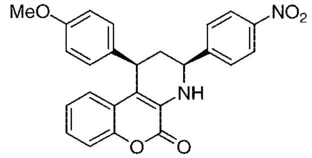
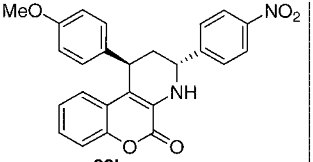
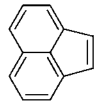
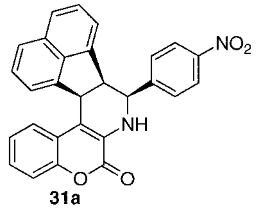
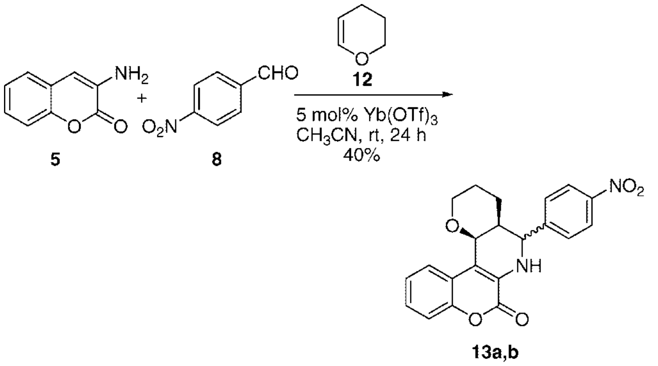
Entry	Dienophile	Reaction time, temperature	Products	*endo/exo* ratio[a]	Yield (%)[b]
1	 **12**	20 min, rt	 **13a**  **13b**	36:64	90
2	 **14**	10 min, rt	 **15a**  **15b**	44:56	72
3	 **16**	7 h, reflux	 **17a**  **17b**	25:75	61
4	 **18**	1 h, rt	 **19a**  **19b**	64:36	81
5	 **20**	25 min, rt	 **21a**  **21b**	37:63	25
6	 **22**	8 h, reflux	 **23a**	>95:5	85
7	 **24**	4.5 h, rt	 **25b**	8:92	82
8	 **26**	5 min, reflux	 **27a**	>95:5	82

TABLE 1. Continued

Entry	Dienophile	Reaction time, temperature	Products	*endo/exo* ratio[a]	Yield (%)[b]
9	 **28**	20 min, rt	 **29a**  **29b**	75:25	82
10	 **30**	18 h, rt	 **31a**	>95:5	61

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixtures. [b] Isolated yields.

SCHEME 5. One-Pot Povarov Reaction



5 **8** **12** **13a,b**

a one-pot operation, in which the diene would be formed in situ from 3-aminocoumarin and an aldehyde, was investigated. Indeed, the reaction of 3-aminocoumarin (**5**), 4-nitrobenzaldehyde (**8**), and DHP (**12**) in the presence of 5 mol % Yb(OTf)$_3$ afforded Povarov adducts **13a,b** in a ratio (39:61) similar to that for the reaction of diene **9** with DHP (**12**) (36:64), but with a lower yield (40% versus 90%) (Scheme 5). Other products were observed by TLC analysis, but none of these could be obtained in pure form. The ^{1}H NMR spectrum of the crude product of this reaction (see Supporting Information) and those of subsequent three-component Povarov reactions typically did not afford much (or any) information as to the structure of the other products. The possibility that water generated during the formation of 2-azadiene **9** might have adversely affected the yield was ruled out when a similar yield (42%) of Povarov adducts **13a**,**b** was obtained when the same reaction was performed in the presence of anhydrous MgSO$_4$.

The effect of the Lewis acids and solvent on the yield and diastereoselectivity of the one-pot reaction was then investigated (Table 2). To this end, a set of reactants was required, the products of which would be easily separable from the side products so that the isolated yields and diastereomeric ratios could be determined easily. After some experimentation, it was found that the reaction between 3-aminocoumarin (**5**), 2-naphthaldehyde (**32**), and DHP (**12**) met this criterion. Under the previously employed conditions (Table 1), two diastereomeric products, **33a** and **33b**, were isolated in a 21:79 ratio in 56% combined yield (Scheme 6).

Kobayashi and co-workers have shown that various lanthanide metal salts catalyze the Povarov reaction.[6] Therefore, the performance of Dy(OTf)$_3$ (entry 2) and CeCl$_3$·7H$_2$O (entry 3) were also evaluated in the one-pot reaction. Neither of these catalysts fared better than the original choice, Yb(OTf)$_3$. Lower yields (28% and 25%, respectively) and poor diastereselectivity (43:57 and 38:62, respectively) were obtained. The yields increased with an increase in the oxophilic character (according to the oxophilicity scale developed by Imamoto and co-workers)[24] of lanthanide salts. This finding was in agreement with previous reports on the activity of various lanthanide salts as Lewis acids.[25] Following the reports of the use of cheap and environmentally benign catalysts for the parent Povarov reaction, we also studied the effect of catalysts such as molecular iodine (I$_2$)[7n,o] (entry 7), potassium hydrogen sulfate (KHSO$_4$)[7d] (entry 6), and silica gel.[26] Silica gel did not catalyze the reaction at room temperature or reflux (entries 4 and 5). Conversely, I$_2$ and KHSO$_4$ afforded yields and diastereoselectivities comparable to those obtained using Yb(OTf)$_3$.

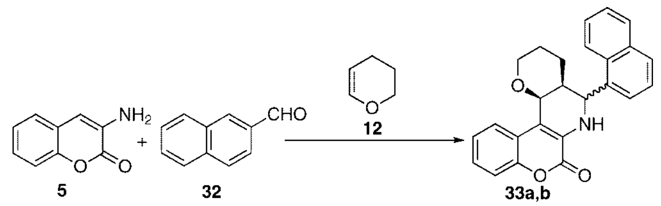
Using Yb(OTf)$_3$ as the Lewis acid, the effect of solvent was then investigated. A low yield (10%) and no diastereoselectivity (50:50) were observed for CHCl$_3$ (entry 11). Although very good diastereoselectivity (~1:9) was achieved in polar protic solvents (methanol and methanol/water), the reaction was very slow. Traces of one of the starting materials, 3-aminocoumarin (**5**), were present in the reaction (by TLC analysis) even after refluxing for 24 and 48 h, respectively (entries 12 and 13). The addition of methanol and/or water to the C=N bond of the 2-azadiene may be responsible for the slow reaction of the azadiene. The use of a somewhat less polar solvent, THF (entry 14), or THF with water as a cosolvent (entry 15) did not improve the yields (41% and 16%, respectively) as compared to acetonitrile. It is not obvious why the yield dropped off when water was a cosolvent, but it does not appear to be attributable to any reaction between water and the adducts. Stirring a mixture

---

(24) Imamoto, T.; Nishiura, M.; Yamanoi, Y.; Tsuruta, H.; Yamaguchi, K. *Chem. Lett.* **1996**, 875–876.

(25) For representative examples, see: (a) Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159–161. (b) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083–4084.

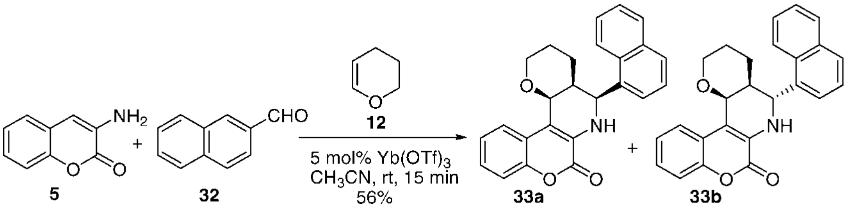
TABLE 2. Effect of Catalyst and Solvent on Povarov Reaction of 5 with 32 and 12



entry	catalyst	solvent	temp	*endo*/*exo* ratio[a]	combined yield (%)[b]
1	5 mol % Yb(OTf)$_3$	CH_3CN	rt	21:79	56
2	5 mol % Dy(OTf)$_3$	CH_3CN	rt	43:57	28
3	10 mol % $CeCl_3 \cdot 7H_2O$	CH_3CN	rt	38:62	25
4	silica gel	CH_3CN	rt		noreaction
5	silica gel	CH_3CN	reflux		noreaction
6	40 mol % $KHSO_4$	CH_3CN	rt	18:82	52
7	30 mol % I_2	CH_3CN	rt	28:72	53
8	5 mol % Yb(OTf)$_3$	CH_3CN	0 °C	15:85	44
9	5 mol % Yb(OTf)$_3$	CH_3CN	−20 °C	9:91	19
10	5 mol % Yb(OTf)$_3$	CH_3CN	−30 °C	$\leq$5:95	7
11	5 mol % Yb(OTf)$_3$	$CHCl_3$	rt	50:50	10
12	5 mol % Yb(OTf)$_3$	MeOH	reflux	12:88	45
13	5 mol % Yb(OTf)$_3$	MeOH/H_2O	reflux	8:92	46
14	5 mol % Yb(OTf)$_3$	THF	rt	24:76	41
15	5 mol % Yb(OTf)$_3$	THF/H_2O	rt	53:47	16
16	5 mol % Yb(OTf)$_3$	toluene	rt	38:62	28
17	5 mol % Yb(OTf)$_3$	DMF	rt		noreaction

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields.

SCHEME 6. One-Pot Povarov Reaction between 3-Aminocoumarin (5), 2-Naphthaldehyde (32), and DHP (12)



of adducts **33a**,**b** in THF/water in the presence of 5 mol % Yb(OTf)$_3$ at room temperature for 1 h and then reflux for 1 h resulted in the formation of no new products according to TLC analysis. In a nonpolar solvent, toluene, a low yield (28%) and a low diastereomeric ratio (38:62) were obtained (entry 16), whereas in a polar aprotic solvent, DMF, the reaction did not proceed appreciably after 2 h at room temperature. Except for $CHCl_3$ and DMF, the yields increased with an increase in the dielectric constant of the solvent (when the reactions were run without a cosolvent). Thus, acetonitrile proved to be the best among the solvents screened.

On the basis of the results of the solvent study, some comments can be made on the mechanism. If a stepwise mechanism is in operation, a product arising from the nucleophilic addition of methanol to an intermediate oxonium ion would be expected.[6b,7x] No such product was isolated from the above reactions (entries 12 and 13). Moreover, the yield of the Povarov adducts was not significantly affected. These observations suggest that, in contrast to the Povarov reactions of aniline-derived 2-azadienes, the Povarov reactions of 2-azadiene **9** most likely proceed through a concerted, yet asynchronous, mechanism. The difference in mechanism may be a consequence of the considerably weaker aromatic character of the 2-pyrone unit in coumarin-derived azadienes compared to that in the benzene ring of aniline-derived azadienes. In other words, a concerted reaction of an aniline-derived azadiene would be disfavored more than the corresponding reaction of a coumarin-derived azadiene because of a greater loss of aromatic stabilization energy in going from the ground state to the transition state.

As anticipated, the diastereomeric ratio could be improved by lowering the temperature, but this occurred at the expense of the yield (entries 8−10). Yields of 44%, 19%, and 7% were obtained when the reactions were performed at 0, −20, and −30 °C, respectively. At −30 °C, the reaction was quite sluggish and 54% of the starting 3-aminocoumarin (**5**) was recovered after running the reaction for 4 h.

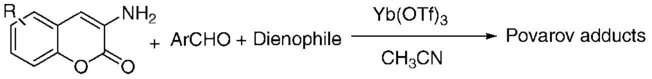
On the basis of the preceding optimization studies, it was decided to test the scope of the one-pot reaction by varying the three components. To begin with, the aldehyde component, which provides C-1 of the azadiene and the substituent attached to it, was varied while the 3-aminocoumarin (**5**) and the dienophile (DHP) were kept constant (Table 3). The conditions used for the synthesis of **33a,b** (entry 1) were employed. Application of a heterocyclic aldehyde, 3-formylcoumarin (**34**),[27] in the three-component reaction with 3-aminocoumarin (**5**) and DHP (**12**) in presence of Yb(OTf)$_3$ in acetonitrile (entry 2) proceeded smoothly at room tem-

---

(26) For examples of silica gel as a Lewis acid, see: (a) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490–3499. (b) March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron* **2000**, *56*, 3603–3609. (c) Kim, D.-K.; Lee, N.; Kim, Y.-W.; Chang, K.; Kim, J. S.; Im, G.-J.; Choi, W.-S.; Jung, I.; Kim, T.-S.; Hwang, Y.-Y.; Min, D.-S.; Um, K.-A.; Cho, Y.-B.; Kim, A. H. *J. Med. Chem.* **1998**, *41*, 3435–3441.

(27) Pottie, I. R. Ph.D. Dissertation, Memorial University of Newfoundland, 2002.

TABLE 3. **Three-Component Synthesis of Pyrido[2,3-*c*]coumarins**



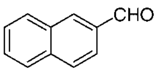
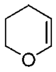
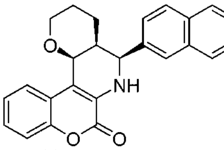
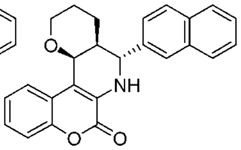
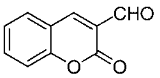
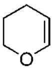
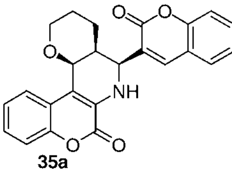
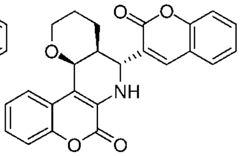
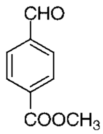
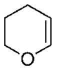
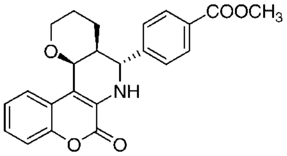
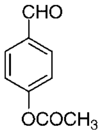
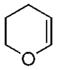
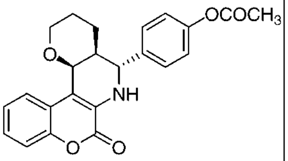
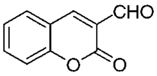
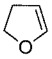
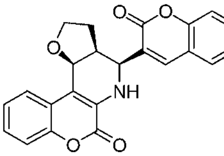
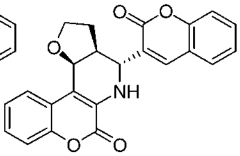
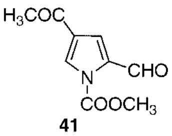
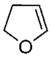
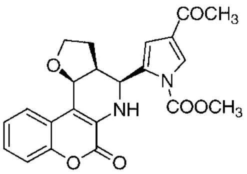
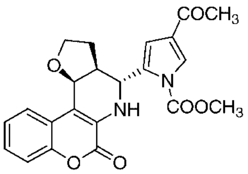
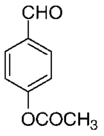
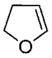
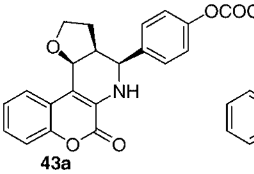
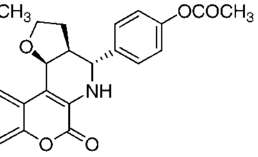
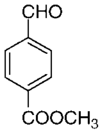
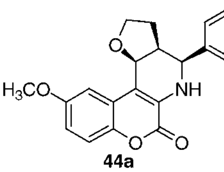
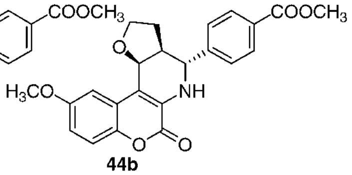
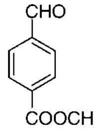
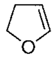
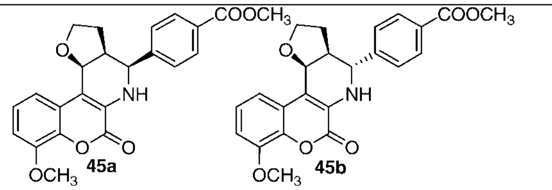
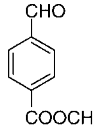
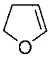
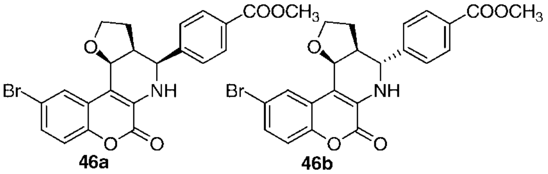
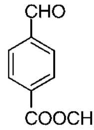
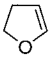
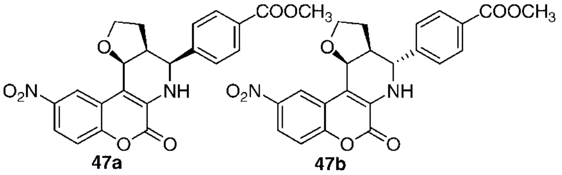
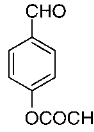
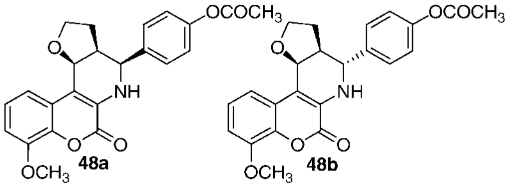
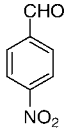
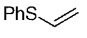
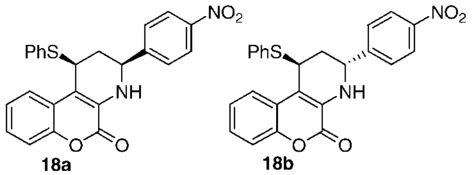
Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio^a	Yield (%)^{b,c}
1	H	 **32**	 **12**	 **33a**  **33b**	21:79	56 (89)
2	H	 **34**	 **12**	 **35a**  **35b**	36:64	71
3	H	 **36**	 **12**	 **37b**	<5:95	54
4	H	 **38**	 **12**	 **39b**	<5:95	26
5	H	 **34**	 **14**	 **40a**  **40b**	42:58	58
6	H	 **41**	 **14**	 **42a**  **42b**	44:56	59
7	H	 **38**	 **14**	 **43a**  **43b**	46:54	33
8	6-OCH$_3$	 **36**	 **14**	 **44a**  **44b**	39:61	34

TABLE 3. Continued

Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio[a]	Yield (%)[b,c]
9	8-OCH_3	 **36**	 **14**	 **45a** **45b**	36:64	34 (54)
10	6-Br	 **36**	 **14**	 **46a** **46b**	44:56	30 (19)
11	6-NO_2	 **36**	 **14**	 **47a** **47b**	42:58	28 (19)
12	8-OCH_3	 **38**	 **14**	 **48a** **48b**	38:62	60
13	H	 **8**	 **18**	 **18a** **18b**	59:41	38

[a] Diastereomeric ratios were determined by ^1H NMR analysis of crude mixtures. [b] Isolated yields are listed. [c] Numbers in parentheses represent yields obtained by using 1.00:1.05:10.0 ratio of amine:aldehyde:dienophile and 10 mol % catalyst.

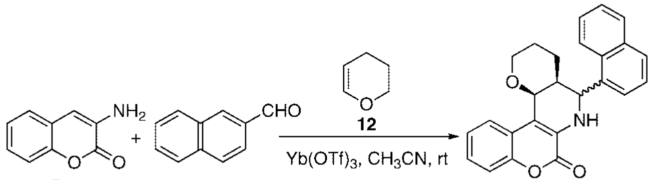
perature to afford tetrahydropyrido[2,3-*c*]coumarins **35a,b** in a ratio of 36:64 in favor of the *exo* diastereomer and 71% combined yield. The more electron-deficient nature of the aldehyde **34** (compared to aldehyde **32**) appeared to have a positive effect on the yield of the Povarov adducts. When 3-aminocoumarin was reacted with methyl 4-formylbenzoate (**36**) and DHP (**12**), Povarov adduct **37b** was obtained with very high selectivity (<5:95) in 54% yield (entry 3). By the same token, very high selectivity (≤5:95) in favor of the *exo* diastereomer was obtained when 3-aminocoumarin (**5**) was reacted with 4-acetoxybenzaldehyde (**38**) and DHP (**12**) to afford Povarov adduct **39b**. However, the yield was only 26% (entry 4). The mild electron-donating ability of the acetoxy group in 4-acetoxybenzaldehyde, which would be expected to attenuate the electron-deficient nature of the in situ formed 2-azadiene, might be responsible for the low yield. For the highest-yielding reaction in the above set of reactions (entry 2), changing the dienophile from DHP (**12**) to DHF (**14**) resulted in the formation of Povarov adducts **40a,b** in 58% yield. The diastereoselectivity (42:58) was close to that observed when DHP was used (cf. entries 2 and 5). Employment of ketone-containing heterocyclic aldehyde **41**[28] afforded Povarov adducts **42a,b** in relatively good yield (59%, entry 6). Isolation of the *endo* diastereomer was very difficult in this reaction. Only the *exo* diastereomer **42b** could be isolated in pure form. This experiment also demonstrated that the three-component reaction could be performed in the presence of a potentially competitive ketone functionality. When 4-acetoxybenzaldehyde was employed, a low yield (33%) and poor diastereoselectivity (46:54) were obtained (entry 7). The reaction had to be heated at reflux for 2.5 days to achieve complete consumption of the starting 3-aminocoumarin.

The 3-aminocoumarin was then varied while the dienophile (DHF) and the aldehyde (methyl 4-formylbenzoate) were kept constant. In general, all of these reactions afforded low yields and diastereoselectivities (entries 8−11). In most cases, the 3-aminocoumarins bore an electron-donating substituent on the carbocyclic ring, which would be expected to deactivate the

---

[28] Prepared from 4-acetylpyrrole-2-carboxaldehyde by reaction with NaH and methyl chloroformate. For the preparation of 4-acetylpyrrole-2-carboxaldehyde, see: Anderson, H. J.; Loader, C. E.; Foster, A. *Can. J. Chem.* **1978**, *58*, 2527–2530.

TABLE 4. Effect of Catalyst Loading, Concentration of 5, and Ratio of Dienophile on Yield



5 **32** **33a,b**

entry	$Yb(OTf)_3$ (mol %)	concn of **5**, ratio of dienophile (equiv)	*endo*/*exo* ratio[a]	combined yield (%)[b]
1	5	0.10 M, 3.0	21:79	56
2	10	0.10 M, 3.0	26:74	74
3	15	0.10 M, 3.0	18:82	72
4	20	0.10 M, 3.0	24:76	71
5	10	0.10 M, 5.0	22:78	84
6	10	0.10 M, 10.0	21:79	89
7	10	0.10 M, 15.0	19:81	87
8	10	0.10 M, 20.0	22:78	86
9	10	0.05 M, 10.0	22:78	89
10	10	0.25 M, 10.0	21:79	88
11	10	0.50 M, 10.0	21:79	84

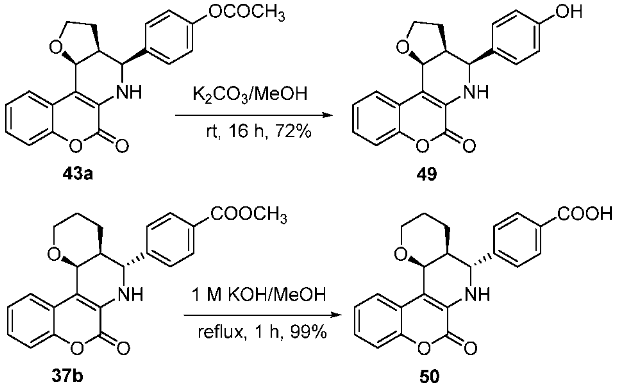
[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields.

diene. However, surprisingly, the reaction involving 3-amino-6-nitrocoumarin (entry 11) afforded the lowest yield of all (28%). In this case, the formation of the 2-azadiene may have been retarded. The reaction of 3-amino-8-methoxycoumarin and 4-acetoxybenzaldehyde (**38**) with DHF under the same reaction conditions (entry 12) afforded a 60% yield of the Povarov adducts **48a,b** in a 38:62 ratio.

Phenyl vinyl sulfide, when reacted with 3-aminocoumarin (**5**) and 4-nitrobenzaldehyde (**8**), afforded a mixture (59:41) of the diastereomeric Povarov adducts **18a,b** in 38% yield (entry 13). It is interesting to note that the formation of the *endo* diastereomer is preferred in this reaction. Also, the yield of this reaction was low compared to the Povarov reaction performed on azadiene **9** with phenyl vinyl sulfide as a dienophile (cf. entry 4, Table 1 and entry 13, Table 2). In general, the reaction times were usually short and yields were satisfactory for the above set of aldehyde and dienophile components with the parent 3-aminocoumarin (**5**). However, attempted variation of the 3-aminocoumarin component resulted in poor yields (entries 8−11). In most cases, small amounts of one or more side products were observed by TLC analysis and were even isolated during chromatography. However, their ^{1}H NMR spectra were complex (see Supporting Information for an example) and could not be reasonably interpreted. Their mass spectra were also complicated but often contained major signals corresponding to M-2 or M-4 for the Povarov adducts. Some intractable materials were also generated. Self-reaction of the in situ formed azadienes may be responsible for this result.[29]

At this stage, other parameters, i.e., the effect of catalyst loading, ratios of the reactants, and the effect of concentration on the yield, were investigated. For this purpose, a reaction having the following features was desired: (1) the two diastereomeric products should be easily separable from other side products by flash chromatography, (2) the reaction time should be short, and (3) the aldehyde should be commercially available. The reaction between 3-aminocoumarin (**5**), 2-naphthaldehyde (**32**), and 3 equiv of DHP (Table 4, entry 1) again met these criteria. The yield of the Povarov adducts was considerably improved (74%) when 10 mol % $Yb(OTf)_3$ was used (entry 2).

SCHEME 7. Reactions of Povarov Adducts 43a and 37b



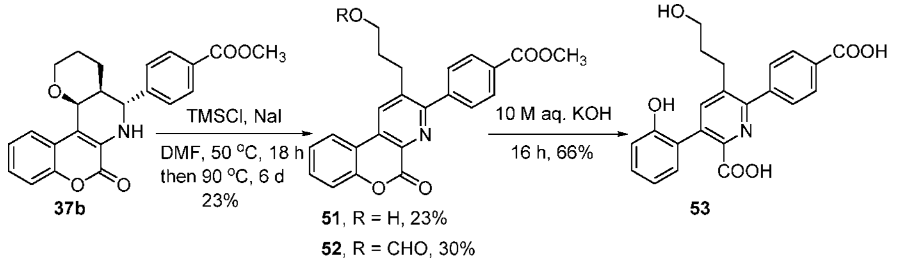
A further increase in the catalyst loading did not improve the yields (entries 3 and 4). Increasing the number of equivalents of DHP to 5 and then 10 resulted in an increase in the yield of the Povarov adducts (84% and 89%, entries 5 and 6, respectively). A further increase in the number of equivalents of the dienophile did not have any further beneficial effect on the yield (entries 7 and 8). Also, the yields were not significantly affected by the changes in concentration of 3-aminocoumarin (**5**) (entries 9−11). Thus, a few of the reactions listed in Table 3 were repeated with the new reaction conditions, i.e., a 1.00:1.05:10.0 ratio of 3-aminocoumarin/aldehyde/dienophile with 10 mol % $Yb(OTf)_3$. The observation that the yield increased in two cases (entries 1 and 9, Table 3) and decreased in two cases (entries 10 and 11, Table 3) suggested that optimal conditions may be somewhat case-specific for the one-pot Povarov reaction.

To ascertain whether the Povarov adducts can equilibrate, *endo* diastereomer **40a** was resubjected to the original reaction conditions, i.e., 5 mol % $Yb(OTf)_3$ in acetonitrile. No signs of conversion to the *exo* diastereomer (**40b**) were observed at room temperature (3 h) or after 24 h at reflux. Also, a 50:50 mixture of diastereomers **40a,b** did not change the ratio when heated to reflux in acetonitrile in the presence of 5 mol % $Yb(OTf)_3$. These results suggest that either the tautomerization step is not reversible under these conditions or that the tautomerization is reversible and the IEDDA reaction, whether concerted or stepwise,[6b] is not. Finally, X-ray quality crystals for *exo*

---

[29] Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *ARKIVOC* **2007**, 129–144.

SCHEME 8. Synthesis of a Terphenyl-Type Compound 53

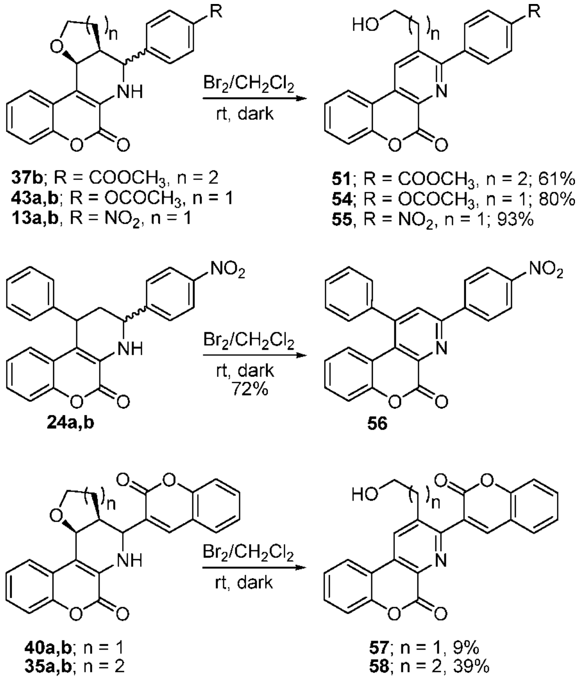


diastereomer **33b** were obtained. A single crystal X-ray structure determination confirmed that the NMR-based assignments of the relative stereochemistry were correct (see Supporting Information).

With a set of relatively complex molecules (tricyclic and tetracyclic heterocycles with 2−3 stereogenic centers) in hand, some aspects of their chemistry were then investigated. Access to free hydroxy or carboxylic acid functional groups might be useful for water solubility and further synthetic transformations. In this context, compound **43a** was chemoselectively hydrolyzed with K_2CO_3/MeOH to afford phenol **49** in 72% yield (Scheme 7). Similarly, ester **37b** was chemoselectively hydrolyzed to afford carboxylic acid **50** in 99% yield. Interestingly, when **37b** was subjected to anydrous demethylation conditions, i.e., TMSCl/NaI,[30] the desired carboxylic acid **50** was not formed. After heating at 50 °C in DMF for 18 h and then 150 h at 90 °C, 10% of the starting material **37b** was recovered after flash chromatography along with two new products. One of the products was pyrido[2,3-*c*]coumarin **51** (R = H), which was presumably formed by an elimination/dehydrogenation process. It was then hydrolyzed with 10 M KOH to afford the ring-opened terphenyl-type product **53** (Scheme 8). The other new product was the formate ester **52** (R = CHO), which could form from **51**, or one of its precursors, via a Vilsmeier−Haack-like O-formylation.

The observation that Povarov adduct **37b** could be converted into the corresponding pyrido[2,3-*c*]coumarin, a rather uncommon heteroaromatic system,[31] provided incentive to investigate more efficient ways of achieving this transformation. The treatment of Povarov adducts with an oxidizing agent, e.g., bromine, would be expected to bring about aromatization of the nitrogen-containing ring through a series of addition and elimination reactions.[32] Accordingly, **37b** was reacted with Br_2 in the dark. Aromatized product **51** was isolated in 61% yield after 1 h. An internal elimination reaction, which opened the tetrahydropyran ring, occurred during the aromatization process. Similarly, Povarov adducts **43a,b**, **13a,b**, and **24a,b** were converted into the corresponding pyrido[2,3-*c*]coumarins **54** (80%), **55** (93%), and **56** (72%), respectively, by the action of Br_2/CH_2Cl_2 in the dark (Scheme 9). However, only 9% and 39% yields of the pyrido[2,3-*c*]coumarins **57** and **58** were obtained from the reactions (Scheme 9) of Povarov adducts **40a,b** and **35a,b**, respectively. The low yields are presumably due to the presence of an additional coumarin unit, which may react unproductively with Br_2.[33]

SCHEME 9. Aromatization of Povarov Adducts



Other aromatization methods were then screened. When compounds **40a,b** were refluxed with Pd/C in xylenes, the reaction was very sluggish. Only traces of the pyrido[2,3-*c*]coumarin **57** were observed by TLC analysis after 6 days at reflux. Acetic acid has been known to accelerate such dehydrogenations.[34] Therefore, the dehydrogenation was attempted with acetic acid as the solvent. Again, only traces of the product were observed (TLC analysis) under these conditions. Another commonly used reagent for carrying out dehydrogenations is DDQ.[35] Heating the Povarov adducts **40a,b** with DDQ in benzene at reflux afforded pyrido[2,3-*c*]coumarin **57** and traces of another product, which could not be obtained in pure form.

---

(30) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874–875.

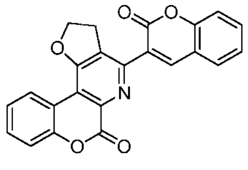
(31) (a) Majumdar, K. C.; Chattopadhyay, B.; Taher, A. *Synthesis* **2007**, 3647–3652. (b) Markey, M. D.; Fu, Y.; Kelly, R. *Org. Lett.* **2007**, *9*, 3255–3257. (c) Rivkin, A.; Adams, B. *Tetrahedron Lett.* **2006**, *47*, 2395–2398. (d) Pavé, G.; Chalard, P.; Viaud-Massuard, M.-C.; Troin, Y.; Guillaumet, G. *Synlett* **2003**, 987–990. (e) Prasad, K. R.; Darbarwar, M. *Synth. Commun.* **1992**, *22*, 2479–2490. (f) Sagi, M.; Wada, K.; Konno, S.; Yamanaka, H. *Heterocycles* **1990**, *30*, 1009–1021. (g) Tabakovic, K.; Tabakovic, I.; Juric, A. *J. Heterocycl. Chem.* **1980**, *17*, 801–803. (h) Khan, M. A.; Gemal, A. L. *J. Heterocycl. Chem.* **1977**, *14*, 1009–1012.

(32) (a) Aksenov, A. V.; Demidova, N. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 913–917. (b) Samoshin, V. V.; Kudryavtsev, K. V. *Tetrahedron Lett.* **1994**, *35*, 7413–7414. (c) Caputo, R.; Ferreri, C.; Palumbo, G.; Russo, F. *Tetrahedron* **1991**, *47*, 4187–4194.

(33) (a) Chaudhuri, S. K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* **2007**, *37*, 271–274. (b) Kothurkar, S.; Shinde, D. B. *Bioorg. Med. Chem. Lett.* **2006**, 6181–6184. (c) Lele, S. S.; Sethna, S. *J. Sci. Ind. Res.* **1955**, *14B*, 101–104. (d) Lele, S. S.; Parikh, R. J.; Sethna, S. *J. Indian Chem. Soc.* **1953**, *30*, 610–616. (e) Dalvi, V. J.; Sethna, S. *J. Indian Chem. Soc.* **1949**, *26*, 359–365.

(34) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955–3957.

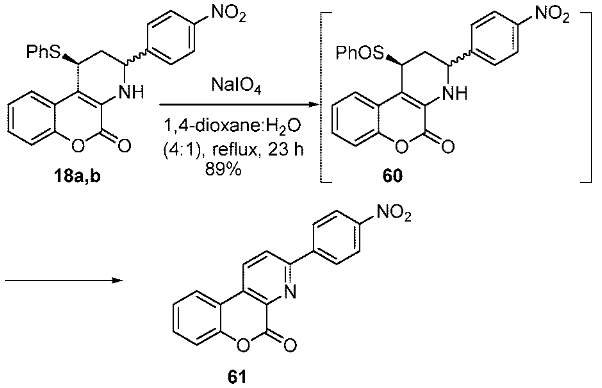
(35) Vanden Eynde, J. J.; Delfosse, F.; Mayence, A.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 6511.



59

FIGURE 1. A possible side product **59** from conversion of **40a,b** to **57** using DDQ.

SCHEME 10. Synthesis of 61 by Oxidation/*syn* Elimination/Dehydrogenation



^{1}H NMR and LC/MS analysis of this impure and poorly soluble compound were consistent with the aromatized compound **59** (Figure 1). Following a procedure by Hartmann et al.,[36] in which nitrous gases were used for preparation of 1,2,4,5-tetrazines from corresponding dihydrotetrazines, a stream of nitrous gases was passed through a solution of **40a,b** in CH_2Cl_2. Gratifyingly, the desired product **57** was formed in 90% yield. Other oxidizing agents, i.e., MnO_2[37] and CAN,[38] also delivered **57**, but the yields were lower (MnO_2, 24% and CAN, 21%) and the reactions were considerably slower.

Povarov adducts formed by using phenyl vinyl sulfide as a dienophile have been converted into quinolines by an oxidation ($NaIO_4$) and thermolysis of the resulting sulfoxide.[39] Treatment of **18a,b** with $NaIO_4$ at room temperature did not show any signs of reaction (by TLC analysis). However, pyrido[2,3-*c*]coumarin **61** was obtained when the reaction mixture was heated at reflux for 23 h. Presumably, the first step in this conversion is the oxidation of the sulfide to the sulfoxide **60**, which then undergoes a *syn* elimination reaction (Scheme 10). The resulting diene is then oxidized to form the aromatized product.

In conclusion, preformed or in situ generated 2-azadienes derived from the condensation of 3-aminocoumarins and aromatic aldehydes take part in the Povarov reaction to afford 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins. The available evidence points toward a concerted asynchronous IEDDA cycloaddition rather than a stepwise cyclization during the Povarov reaction. The multicomponent version of this reaction provides rapid access to unusual tricyclic and tetracyclic heterocycles. The corresponding pyrido[2,3-*c*]coumarins can be formed upon oxidation of the Povarov adducts with various oxidizing agents. Further applications of this methodology to the synthesis of complex heterocycles will be disclosed in due course.

Experimental Section

Typical Experimental Procedure. (4a*S,5*S**,12c*S**)-5-(4-Nitrophenyl)-3,4,4a,5,6,12c-hexahydro-7*H*-1,8-dioxa-6-aza-2*H*-pyrano[5,6-*c*]phenanthren-7-one (13a) and (4a*S**,5*R**,12c*S**)-5-(4-Nitrophenyl)-3,4,4a,5,6,12c-hexahydro-7*H*-1,8-dioxa-6-aza-2*H*-pyrano[5,6-*c*]phenanthren-7-one (13b).** To a solution of diene **9** (0.50 g, 1.7 mmol) and $Yb(OTf)_3$ (0.05 g, 5 mol %) in acetonitrile (10 mL) was added DHP (0.50 mL, 5.1 mmol, 0.43 g). The reaction mixture was stirred for 20 min at room temperature. The thick yellow suspension turned into a bright yellow suspension over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue. The dr was determined to be 36:64 in favor of **13b** by ^{1}H NMR analysis of the crude reaction mixture. The residue was then subjected to flash chromatography (dichloromethane), which afforded **13a** (0.15 g, 25%) as a yellow solid and **13b** (0.39 g, 1.1 mmol, 65%) as a yellow solid. Combined yield of Povarov adducts = 0.62 g, 1.6 mmol, 90%. **13a**: mp = 228−229 °C (chloroform/hexane). δ_{H} ($CDCl_3$) = 8.27 (d, 2H, *J* = 9.1 Hz, H-3′), 8.21 (d, 1H, *J* = 7.6 Hz, H-12), 7.63 (d, 2H, *J* = 8.7 Hz, H-2′), 7.37−7.34 (m, 2H), 7.30−7.28 (m, 1H), 5.50 (d, 1H, *J* = 4.7 Hz, H-12c), 5.07 (s, 1H, H-6), 4.81 (d, 1H, *J* = 2.5 Hz, H-5), 3.65−3.64 (m, 1H, H-2α), 3.25 (td, 1H, *J* = 11.0, 1.2 Hz, H-2*β*), 2.38−2.35 (m, 1H, H-4a), 1.76−1.67 (m, 1H), 1.59−1.48 (m, 1H), 1.43−1.41 (m, 2H) ppm. δ_{C} ($CDCl_3$) = 158.5 (C-7), 148.5, 147.9, 147.2, 130.7, 128.0 (C-3′), 127.1, 125.1, 124.8 (C-12), 124.1 (C-2′), 120.3, 116.7, 116.6, 71.8 (C-12c), 62.9 (C-2), 58.9 (C-5), 38.3 (C-4a), 24.3 (C-3), 19.7 (C-4) ppm. IR ν = 3340 (w), 2854 (w), 1722 (s), 1618 (w), 1598 (w), 1516 (m), 1348 (s), 1181 (m), 1091 (s), 857 (m), 752 (s) cm^{-1}. HRMS *m*/*z* [M$^+$] calcd for $C_{21}H_{18}N_2O_5$ 378.1214, found 378.1225. **13b**: mp = 263−264 °C (chloroform/hexane). δ_{H}($CDCl_3$) = 8.27 (d, 2H, *J* = 9.4 Hz, H-3′), 7.62 (d, 2H, *J* = 8.2 Hz, H-2′), 7.57−7.55 (m, 1H, H-12), 7.29−7.27 (m, 3H), 5.09 (s, 1H, H-6), 4.87 (d, 1H, *J* = 11.4 Hz, H-5), 4.71 (d, 1H, *J* = 3.5 Hz, H-12c), 4.20−4.17 (m, 1H, H-2α), 3.82 (td, 1H, *J* = 11.6, 1.7 Hz, H-2*β*), 2.12−2.08 (m, 1H, H-4a), 1.94−1.78 (m, 2H), 1.48−1.46 (m, 2H) ppm. δ_{C}($CDCl_3$) = 158.9 (C-7), 148.6, 148.3, 147.9, 130.0 (C-2′), 129.0, 126.8, 125.1, 124.3 (C-3′), 122.0, 120.3, 116.8, 115.4, 69.7 (C-12c), 69.3 (C-2), 54.2 (C-5), 38.9 (C-4a), 23.6 (C-3), 22.0 (C-4) ppm. IR ν = 3389 (w), 2946 (w), 1710 (s), 1633 (m), 1509 (s), 1341 (s), 1186 (m), 1090 (m), 752 (s) cm^{-1}. HRMS *m*/*z* [M$^+$] calcd for $C_{21}H_{18}N_2O_5$ 378.1214, found 378.1230.

One-Pot Procedure. To a clear colorless solution of 3-aminocoumarin (**5**) (0.25 g, 1.6 mmol) in acetonitrile (30 mL) was added 4-nitrobenzaldehyde (**8**) (0.25 g, 1.6 mmol), followed by the addition of $Yb(OTf)_3$ (0.05 g, 5 mol %) and DHP (0.42 mL, 4.6 mmol, 0.39 g). The reaction mixture was allowed to stir at room temperature for 24 h. The progress of the reaction was monitored by TLC. When the reaction was complete, the solvent was removed under reduced pressure, and the yellow residue was subjected to flash chromatography (dichloromethane), which afforded diastereomeric mixture **13a,b** (0.23 g, 40%) as a yellow solid. The dr was determined to be 36:64 in favor of **13b** by ^{1}H NMR analysis of the crude reaction mixture.

Acknowledgment. The Natural Sciences and Engineering Research Council (NSERC) of Canada and AnorMED Inc. are gratefully acknowledged for financial support of this work. We also thank Dr. H. J. Anderson and Dr. C. E. Loader for a sample of 4-acetylpyrrole-2-carboxaldehyde.[25]

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for individual compounds and crystallographic data in CIF format for **33b**, **43a**, and **43b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801411P

---

(36) Hartmann, K.-P.; Heuschmann, M. *Tetrahedron* **2000**, *56*, 4213–4218.

(37) Heravi, M. M.; Moosavi, F. S. Sh.; Beheshtihay, Sh.; Ghassemzadeh, M. *Heterocycl. Commun.* **2004**, *10*, 415.

(38) Pfister, J. R. *Synthesis* **1990**, 689–90.

(39) Demaude, T.; Knerr, L.; Pasau, P. *J. Comb. Chem.* **2004**, *6*, 768–775.