ORGANIC LETTERS

2000
Vol. 2, No. 9
1333−1336

Synthesis of Enamides Related to the Salicylate Antitumor Macrolides Using Copper-Mediated Vinylic Substitution

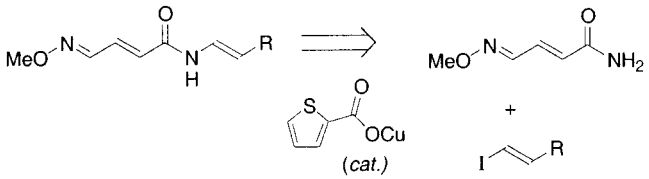
Ruichao Shen and John A. Porco, Jr.*

Department of Chemistry and Center for Streamlined Synthesis, Metcalf Center for Science and Engineering, Boston University, 590 Commonwealth Avenue, Boston Massachusetts 02215

porco@chem.bu.edu

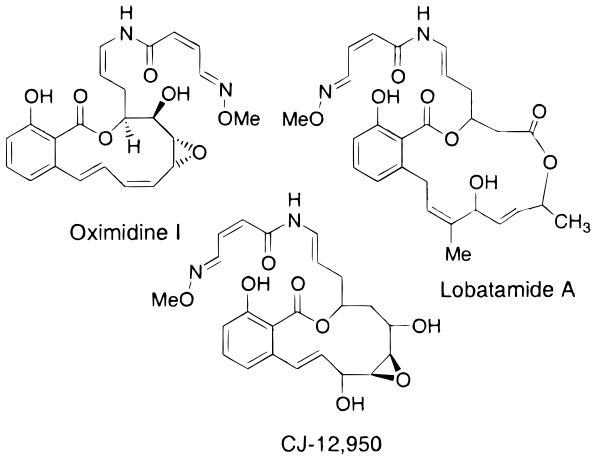
Received March 13, 2000

ABSTRACT



A new approach to the assembly of enamides is described using copper(I) carboxylate-catalyzed substitution of vinyl iodides and amides. Modified reaction conditions have been developed to synthesize the *O*-methyloxime enamide side chains related to the natural products lobatamides A–F, oximidine I and II, and CJ-12 950.

The salicylate enamide macrolides represent a novel class of antitumor natural products with a potentially novel and thus far undetermined mechanism of action. Members of the class include lobatamides A−F,[1] oximidines I and II,[2] salicylihalamide B,[3] CJ-12,950 and CJ-13,357,[4] and apiculatarens A and B.[5,6] As part of a program to synthesize the *O*-methyloxime enamide containing compounds lobatamides and oximidines, we required a general method to synthesize enamides suitable for late-stage introduction.[7] In this Letter, we disclose our initial studies related to the development of copper-catalyzed vinylic substitution of alkenyl iodides and amides which results in the assembly of stereochemically well-defined enamides.



Enamides have been previously synthesized using a number of methods, including the Curtius rearrangement of

(1) (a) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968. (b) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laasko, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. (c) Suzumura et al. have independently isolated YM-75518 which is identical to lobatamide A, see: Suzumura, K.-i.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiamodjo, R. M.; Suzuki, K.-i.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573.

(2) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y. Seto, H. *J. Org. Chem.* **1999**, *64*, 153.

(3) Erickson, K. L.; Beutler, J.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188.

(4) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14.

(5) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

(6) For the synthesis of an enamide-truncated analogue of salicylihalamide A, see: Furstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

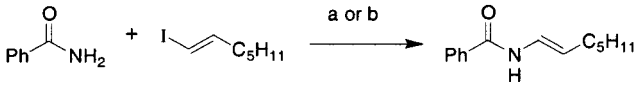
10.1021/ol005800t CCC: $19.00
Published on Web 04/05/2000

α,β unsaturated acyl azides,[7,8] palladium(II)-catalyzed amidation of alkenes,[9] direct addition of amides to alkynes,[10] acylation of imines,[11] acid-catalyzed condensation of aldehydes and amides,[12] amide Peterson olefination,[13] and Horner−Wittig and Wadsworth−Emmons reactions.[14] However, most of these methods are either unable to control *E*−*Z* olefin stereoselectivity or often suffer from low yields, and thus may not be suitable for use at a late stage in a synthesis.

In considering potential methods for the formation of enamides, we have focused our initial efforts on transition metal-catalyzed vinylic substitution reactions of vinyl iodides and amides. Ogawa et al. have reported the copper iodide-promoted substitution of vinyl bromides and potassium amides (1 equiv of CuI, HMPA, 130 °C) to afford enamides in low to moderate (38−45%) yields.[15] On the basis of this precedent, and reports of related copper-catalyzed substitution reactions,[16] our initial goal was to develop a copper-catalyzed method that would occur at milder temperatures and be suitable for the installation of potentially labile enamides.

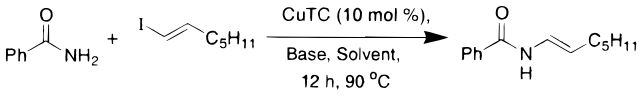
Initial screening of catalyst systems compared phosphine copper(I)[17] and copper(I) carboxylate catalysts using cesium carbonate (Cs_2CO_3) as base (Scheme 1).[16] Enhanced conversions were obtained using Liebeskind's copper(I) thiophenecarboxylate (CuTC)[18] which led us to pursue further reaction optimization using this catalyst. Using benzamide and (*E*)-1-iodoheptene as model substrates, we performed parallel syntheses on the Quest 210 Organic Synthesizer (Argonaut Technologies)[19] as shown in Table 1. These studies established the requirement for polar aprotic solvents in the reaction (NMP or DMSO) and a slight enhancement when using Cs_2CO_3 vs K_2CO_3 as base. Further improvement to >95% conversion was found using 30 mol % of CuTC and rigorous vacuum purge degassing of the reaction mixture prior to heating (90 °C, 12 h). Using these conditions, a number of enamides were synthesized as shown in Table 2.[20] Both styrenyl and alkenyl iodides are workable in the reaction and generally afford isolated yields of enamides in

Scheme 1. Comparison of Copper Catalysts[a]



[a] (a) CuI (0.10 equiv), Cs_2CO_3 (1.2 equiv), PPh_3 (0.20 equiv.), NMP, 90 °C, 12 h, 31 % (^{1}H NMR) (b) CuTC (0.10 equiv), Cs_2CO_3 (1.2 equiv), NMP 90 °C, 12 h, 59 % (^{1}H NMR).

Table 1. Parallel Evaluation of Bases and Solvents

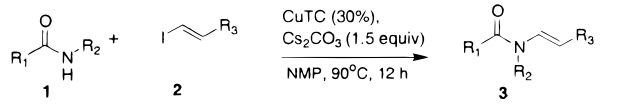


entry	solvent	base	% conv.[a]
1	NMP	Cs_2CO_3	72
2	toluene	Cs_2CO_3	0
3	DMSO	Cs_2CO_3	66
4	dioxane	Cs_2CO_3	0
5	NMP	K_2CO_3	32
6	toluene	K_2CO_3	0
7	DMSO	K_2CO_3	67
8	dioxane	K_2CO_3	0
9	NMP	Cs_2CO_3	13[b]

[a] Determined by ^{1}H NMR
[b] Reaction was conducted at 25 °C

(7) For a recent synthesis of the heptadienamide side chain of salicylihalamide A and apicularens A and B, see: Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407.
(8) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1*. **1988**, 2185.
(9) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 6643.
(10) (a) Mohre, H.; Kilian, R. *Tetrahedron* **1969**, *25*, 5745. (b) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413.
(11) (a) Boeckmann, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250.
(12) (a) Zeeza, C. A.; Smith, M. B. *Synth. Comm.* **1987**, *17*, 729−40. (b) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227.
(13) (a) Cuevas, J.-C.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989,** *30*, 5841. (b) Palomo, C.; Aizpurua, J. M.; Legido, M.; Picard, J. P.; Dunogues, J.; Constantieux, T. *Tetrahedron Lett.* **1992**, *33*, 3903.
(14) (a) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (b) Paterson, I.; Cowden, C.; Watson, C. *Synlett* **1995**, 209.
(15) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443.
(16) (a) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (b) Kiyomori, A.; Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (c) Kalanin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.
(17) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.
(18) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.
(19) http://www.argotech.com/quest (March 27, 2000).
(20) **Typical experimental procedure** (Table 2, entry 2): Sorbamide (83 mg, 0.75 mmol), CuTC (28.6 mg 0.15 mmol), and Cs_2CO_3 (245 mg, 0.75 mmol) were placed in an oven-dried 10 mL Schlenk flask equipped with a stir bar. Anhydrous NMP (2 mL) was added using a dry syringe. The suspension was degassed with high vacuum until gas evolution ceased. (*E*)-1-Iodoheptene (112 mg, 0.5 mmol, 79 μL) was added using a microliter syringe. The mixture was degassed again using high vacuum until no further gas evolution was observed. The suspension was stirred at 90 °C for 12 h under argon. The red slurry was cooled to room temperature and diluted with ether, and the ether extracts were washed with pH 7 buffer. The aqueous layer was extracted 2*x* further with ether. The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated. The pure enamide **3b** was obtained as a white solid (71 mg, 69% yield) after flash chromatography on silica gel (hexane:ethyl acetate = 4:1, 1% Et_3N): mp 116−117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (1H, dd, *J* = 14.8, 10 Hz), 7.16 (1H, d, *J* = 9.6 Hz), 6.82 (1H, dd, *J* = 14, 10.8 Hz), 6.12 (2H, m), 5.71 (1H, d, *J* = 14.8 Hz), 5.16 (1H, dt, *J* = 14, 7.2 Hz), 1.82 (3H, d, *J* = 5.6 Hz), 1.30 (6H, m), 2.01 (2H, m), 0.86 (3H, t, *J* = 6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 163.1, 142.4, 138.6, 129.7, 122.6, 120.7, 113.6, 31.3, 29.7, 29.5, 22.5, 18.6, 14.0 ppm; HRMS (EI) calcd 207.1623, found 207.1588; IR (neat) 3247, 2921, 1654, 1629, 1534, 1350 cm^{-1}.

Table 2. Copper-Catalyzed Enamide Formation



1 2 3

entry	R_1	R_2	R_3	yield (%)[a]
1	Ph	H	C_5H_{11}	71 (**3a**)
2	Me	H	C_5H_{11}	69 (**3b**)
3	H	Me	C_5H_{11}	75 (**3c**)
4	Ph	H	Ph	57 (**3d**)
5	Me	H	Ph	58 (**3e**)
6	H	Me	Ph	70 (**3f**)

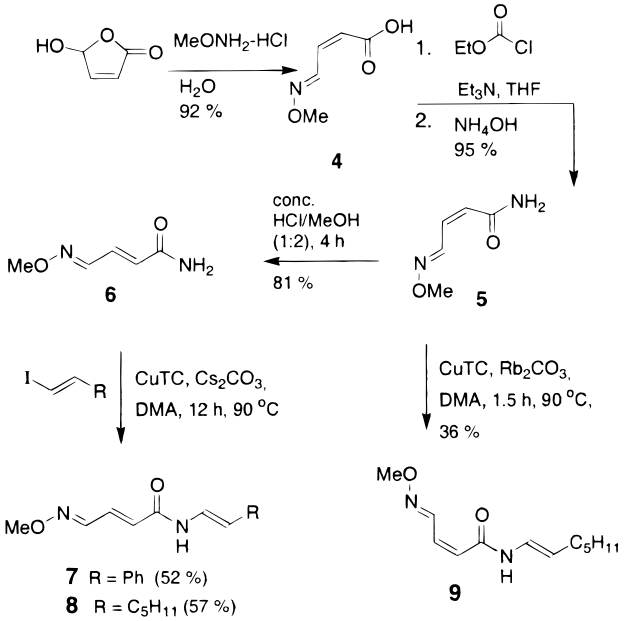
[a] All yields are based on pure materials isolated by silica gel chromatography (hexanes/ethyl acetate using 1 % Et_3N) [b] 3:1 mixture of rotamers by ^{1}H NMR (400 MHz) [c] 1.3:1 mixture of rotamers by ^{1}H NMR (400 MHz)

the 57−75% range. Entries 2 and 5 demonstrate the use of 2,4-hexadienamide[21] as a coupling partner to afford conjugated enamides. Entries 3 and 6 represent efficient syntheses of the *N*-alkenyl-*N*-methylformamide functionality present in the cytotoxic marine macrolides ulapualides and mycalolides.[14b,22]

To prepare enamides related to the salicylate antitumor macrolides, we required (*E*)- and (*Z*)-*O*-methyloxime amides which were prepared as shown in Scheme 2. Treatment of malealdehydic acid with aqueous *O*-methylhydroxylamine hydrochloride led to the formation of (*Z*)-*O*-methyloxime acid **4** (92%).[23] The (*Z*)-*O*-methyloxime amide **5** was prepared in 88% yield by formation of the mixed anhydride of **1** and subsequent reaction with aqueous ammonia. Use of the acid chloride of **4** in this transformation led to the formation of the isomerized (*E*)-*O*-methyloxime amide **6** in low yield. (*Z*)-Amide **5** could be fully isomerized to **6** in 81% yield using concentrated HCl/MeOH (1:2). Treatment of **6** (1.5 equiv) with (*E*)-1-iodoheptene or (*E*)-1-iodostyrene (1.0 equiv) under the previously described conditions (30 mol % of CuTC, 1.5 equiv of Cs_2CO_3, DMA, 90 °C, 12 h) led to the formation of model enamide compounds **7** and **8** (Scheme 2) in isolated yields of 52 and 57%, respectively. However, use of amide **5** under the same conditions led to consumption of vinyl iodide (as determined by ^{1}H NMR) but did not afford an enamide product. In an effort to improve reactions employing (*Z*)-amide **5**, it was found that use of Rb_2CO_3 as base[24] led to the formation of the desired enamide **9** (36%). It was determined by control experiments that (*Z*)-*O*-methyloxime enamide **9** was decomposed by Cs_2CO_3 at high temperature.[25]

Although a detailed mechanistic investigation of the copper carboxylate-mediated vinylic substitution awaits further experimentation, tentative proposals are outlined in Figure 1. In the first scenario (A), a cesium carboxamide may react with CuTC to afford a cuprate-like intermediate which forms the enamide after four-centered *ipso*-substitution of the vinyl iodide. A related mechanism was recently proposed by Buchwald and co-workers to explain the role of cesium in

Scheme 2. Synthesis of *O*-Methyloxime Enamides



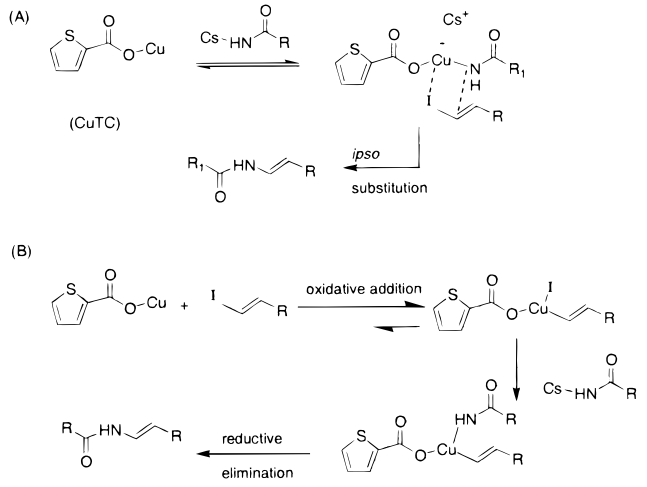


Figure 1. Mechanistic scenarios for copper-catalyzed enamide formation.

(21) Pellegata, R.; Italia, A.; Villa, M. *Synthesis* **1985**, 517.
(22) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235.
(23) For the synthesis of the oxime of malealdehydic acid, see: Schroeter, S. H.; Appel, R.; Brammer, R.; Schenck, G. O. *Justus Liebigs Ann. Chem.* **1966**, *697*, 42.
(24) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.
(25) Further studies are in progress to determine the mode of decomposition of enamide **9** under basic conditions.

copper-catalyzed substitution of aryl halides with phenols.[16a] It is also conceivable that electron-transfer mechanisms are involved in the substitution process.[26] In a second scenario (B), oxidative addition of the vinyl iodide to CuTC occurs which, as proposed by Liebeskind and co-workers, may be favored by use of the carboxylate ligand.[18] Displacement of a copper iodide intermediate by the cesium carboxamide would be followed by reductive elimination to afford the enamide product.

In summary, enamides related to the side chains of the salicylate antitumor natural products have been synthesized using copper(I) carboxylate-catalyzed substitution of vinyl iodides and amides. Extension of these methods to other substrates and application of transition-metal catalyzed vinylic substitution reactions to the synthesis of the lobatamides, oximidines, and unnatural analogues is in progress and will be reported in due course.

(26) (a) Aalten, H. L.; van Koten, G.; Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565. (b) Matyjaszewski, K.; Wei, M.; Xia, J.; Gaynor, S. G. *Macromol. Chem. Phys.* **1998**, *199*, 2289.

Acknowledgment. We thank Professor James Panek and Jennifer Schaus (Boston University) for helpful suggestions. Work at the Boston University Center for Streamlined Synthesis (CSS) is supported by Argonaut Technologies, Boehringer-Ingelheim, Glaxo-Wellcome, and Monsanto-Searle.

Supporting Information Available: Experimental procedures and characterization for compounds **3a**−**f** and **5**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005800T