ORGANIC LETTERS

2008
Vol. 10, No. 2
185−188

Development of a Novel Pd-Catalyzed *N*-Acyl Vinylogous Carbamate Synthesis for the Key Intermediate of ICE Inhibitor VX-765

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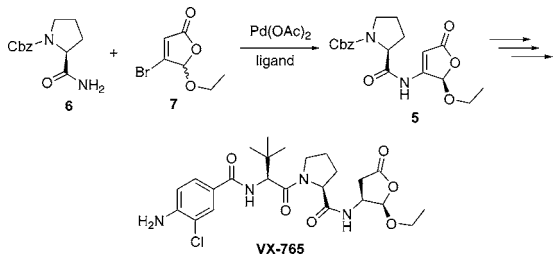
Received October 17, 2007

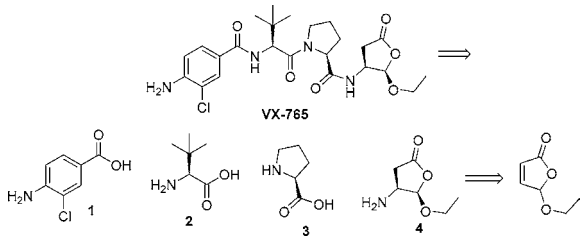
ABSTRACT



A novel Pd-catalyzed coupling of Cbz-protected proline amide with 4-bromo-5-ethoxyfuran-2(5*H*)-one was developed for the synthesis of the P1−P2 unit (5) of VX-765. The process afforded quantitative coupling in the presence of water, providing a 1:1 mixture of 5 and its ethoxy epimer *epi*-5. Compound 5 was isolated as a single diastereomer via fractional crystallization, which was stereoselectively converted to 17 via hydrogenation, and subsequently transformed to VX-765. Nine examples of the Pd coupling are presented with yields ranging from 76−98%.

Interleukin-1 (IL-1) is a pro-inflammatory and immunoregulatory protein which is involved in the pathogenesis of acute and chronic inflammatory and autoimmune diseases.[1] IL-1β, one of two isoforms of IL-1, is converted into its biologically active form by interleukin-1β converting enzyme (ICE) and has been shown to be involved in apoptosis and inflammation.[2] Hence, ICE inhibitors represent a class of compounds useful for the control of such events. VX-765 is an inhibitor of ICE and has been developed for the treatment of ICE-related diseases.[3] VX-765 is a triamide containing one proline (Pro) and one *tert*-Leu (Tle) residue, a 4-amino-3-chlorobenzoic acid unit, and a tetrahydroethoxyfuranone unit. Previous strategies for the synthesis of VX-765 focused exclusively on amide bond formations, leading to the

Scheme 1. Conventional Retrosynthesis of VX-765



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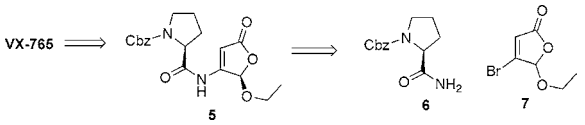
(1) (a) Wood, D. D.; Ihrie, E. J.; Dinarello, C. A.; Cohen, P. L. *Arthritis Rheum.* **1983**, *26*, 975. (b) Pettipher, E. J.; Higgs, G. A.; Henderson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8749. (c) Bataille, R.; Chappard, D.; Bernard, K. *Int. J. Clin. Lab. Res.* **1992**, *21*, 283. (d) Vidal-Vanaclocha, F.; Amezaga, C.; Asumendi, A.; Kaplanski, G.; Dinarello, C. A. *Cancer Res.* **1994**, *54*, 2667.

10.1021/ol702532h CCC: $40.75
Published on Web 12/15/2007

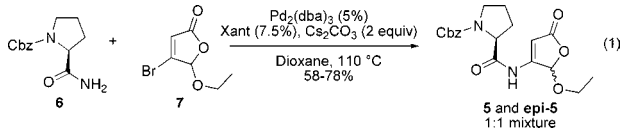
retrosynthetic analysis shown in Scheme 1. Although the Pro, Tle, and the benzoic acid units are readily available starting materials, preparation of aminotetrahydroethoxyfuranone **4** remains difficult and impractical due to its instability and proclivity for undesired side reactions under amide bond-forming conditions. As such, and in order to circumvent the problems associated with **4**, a new approach to VX-765 based on the P1−P2 key intermediate **5** was developed via the disconnections shown in Scheme 2. The process relies on

Scheme 2. Retrosynthesis of VX-765 via Pd-Catalyzed Coupling



formation of the crucial C−N bond of **5** via coupling of the amide Z-Pro-NH_2 and bromoethoxyfuranone, a process that has not been previously demonstrated. We present here a novel target-oriented methodology for the synthesis of **5** via development of a Pd-catalyzed *N*-acyl vinylogous carbamate synthetic methodology.

The coupling of β-halo enoates with amides to generate *N*-acyl vinylogous carbamates is a new process and has been demonstrated previously by Porco using allyl (*E*)-3-iodoacrylates and (*E*)-3-iodoacrylamides in the presence of 1−5 mol % of CuI_2.[4−6] In this case, iodides were required as the substrate and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane as the ligand. In our case, the practicality and ease of accessibility of **7** required a coupling method amenable to (*E*)-3-bromoacrylates, substrates not conducive to Cu-catalyzed conditions. Our initial investigations began with the typical conditions used for Pd-catalyzed amide N-arylations (eq 1). Under these conditions, Z-Pro-NH_2 was coupled to **7** to give **5** and *epi*-**5** in yields ranging from 58 to 78%, capricious results at best. Control experiments showed the irreproducibility arose from the instability of **7** under basic conditions.



To solve the instability problem, a series of experiments were conducted to determine the best base, solvent, temperature, and precatalyst combination to effect the desired coupling reaction. A rapid evaluation of solvents (nonpolar and polar aprotic solvents) and bases showed **7** was stable in the presence of K_2CO_3 or Cs_2CO_3 in toluene at 22−25 °C for 8 h and began to decompose (HPLC) at temperatures of 45−50 °C. Next, we turned our attention to determining the best ligand and palladium source for the coupling.

Table 1 shows the results from evaluating two practical palladium sources and several ligands. The reaction conditions used high catalyst loadings (10 mol %) for rapid coupling in order to minimize bromide decomposition. For $Pd(OAc)_2$, Xantphos, DPEPhos, and DPPF gave the best conversions after 2 h at 60 °C (entries 1,3, and 6); Cy_2P-biphenyl and *t*-Bu_2P-biphenyl gave less than 10% conversion (entries 7 and 8), and BINAP gave only 21% conversion (entry 2). Alkylidene diphenylphosphino ligands gave poor results with DPPE and DPPB, providing 16 and 0% conversion, respectively (entries 4 and 5). Replacing $Pd(OAc)_2$ with Pd_2dba_3 gave comparable results: Xantphos, DPEPhos, and DPPF were the best ligands (entries 1, 3, and 6). Interestingly, BINAP gave nearly identical results for

Table 1. Ligand Evaluation for Coupling in Equation 1[a]

		conversion (%)	
entry	ligand	$Pd(OAc)_2$	$Pd_2(dba)_3$
1	Xantphos	>85	>85
2	BINAP	21	23
3	DPEPhos	47	72
4	DPPB	0.0	7.2
5	DPPE	16	7.4
6	DPPF	72	70
7	Cy_2P-biphenyl	9.8	30
8	*t*-Bu_2P-biphenyl	8.5	42

[a] Conditions: 1.1 equiv of **7**, 10 mol % of Pd source, 15 mol % of ligand, Cs_2CO_3 (1.5 equiv), toluene, 60 °C, 2 h.

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$Pd_2(dba)_3$ and $Pd(OAc)_2$, but Cy_2P-biphenyl and *t*-Bu_2P-biphenyl gave much higher conversions for $Pd_2(dba)_3$. From the data, Xantphos was chosen as the best ligand.

In conjunction with optimization studies, the robustness of the reaction was evaluated by performing the reaction on 100 g scale. Using $Pd_2(dba)_3$ (2.5%), Xantphos (7.5%), Cs_2CO_3 (2 equiv), and **7** (1.1 equiv) in toluene, less than 70% conversion was observed after 3 h of reaction time. Charging an additional 0.5 equiv of **7** and warming the reaction mixture to 105 °C for 8 h resulted in less than 80% conversion. HPLC analysis of the reaction mixture showed the presence of large amounts of **7**. The stability of **7** under these conditions was expressly contrary to our results from the stability study. After cooling the reaction mixture to room temperature and upon adding water for workup, copious amounts of gas evolution (CO_2) was observed, indicative of HBr quenching with Cs_2CO_3. This observation led to the conclusion that the poor solubility of the inorganic base in anhydrous toluene, and possible coating of the base by CsBr generated during the reaction, prevented neutralization of HBr, which consequently inhibited the catalyst and provided the acidic conditions necessary for **7** to remain intact even at high temperatures. The inability of the inorganic base to neutralize HBr was addressed by investigating aqueous conditions.

Two scenarios were envisaged for successful development of the Pd-catalyzed coupling under aqueous conditions. In the first scenario, a 1:1 v/v toluene/water solvent mixture was examined. Under these conditions, using 2.5 equiv of K_2CO_3 as base, the precatalyst generated from $Pd(OAc)_2$ (1 mol %) and Xantphos (1.5 mol %) provided 99% conversion of **6** and **7** to **5** and *epi*-**5** at 50 °C in 5.5−6 h. The use of aqueous conditions resulted in a more rapid decomposition of **7**, which was obviated by slow addition of **7** over 3−3.5 h. The use of $Pd_2(dba)_3$ gave inferior results. However, when the 1:1 toluene/water mixture was replaced by 3 equiv of water and 1 mol % of a phase transfer catalyst (PTC) in toluene, the reaction performed better, giving a 99.5% conversion of **6** to **5** and *epi*-**5** in 3.5−4 h. The use of 3 equiv of water, 1.5 equiv relative to K_2CO_3, was chosen specifically to generate the sesquihydrate $K_2CO_3(H_2O)_{1.5}$. Thus, enough water was present to fully wet the anhydrous base, but not too much to allow for excess water in solution. Additionally, the PTC was used to maintain efficient mass transfer between phases. The superior features of this system can be seen explicitly in Figure 1. After the addition of **7** was complete (3 h), the coupling in the presence of 3 equiv of water continued unabated until complete conversion was obtained (circles). However, in the case of a 1:1 toluene/water mixture, catalyst deactivation began soon after the addition of **7** was complete (diamonds). Although the reaction proceeded to 99% completion, the data show that at 85−90% conversion the rate of reaction significantly decreased.

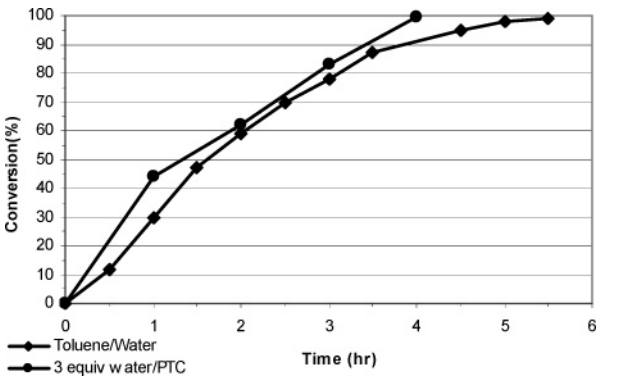


Figure 1. Effect of water content on reaction rate.

The success of the Pd-catalyzed coupling in the presence of 3 equiv of water and PTC prompted further investigations into the nature of the reaction. The optimized conditions for the coupling are shown in eq 2, and the results from monitoring the reaction progress are shown in Figure 2. Of

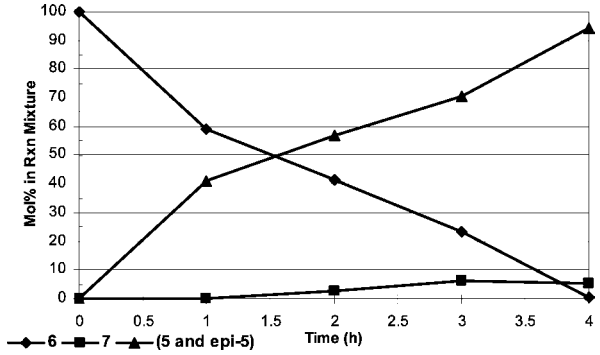
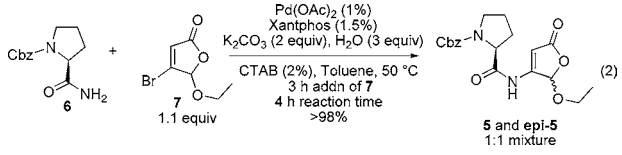


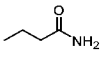
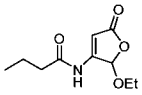
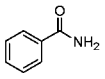
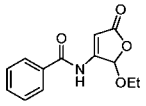
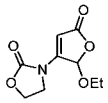
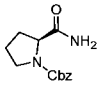
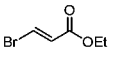
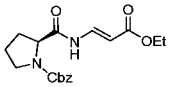
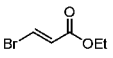
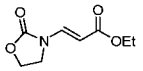
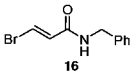
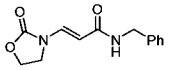
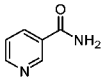
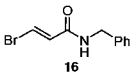
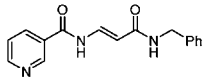
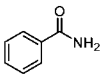
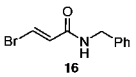
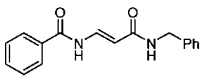
Figure 2. Mol % of components during the course of the reaction.

significant note is that, during the first 2 h of addition, the concentration of **5** and its ethoxy epimer *epi*-**5** rose to 65%, while the concentration of **7** remained below 1%, indicating that decomposition of **7** was significantly slower than coupling to **6**. After the addition of **7** was complete, HPLC analysis showed about 4% of **7** in solution, signifying that 6% of **7** decomposed during the course of the reaction. If the reaction mixture was allowed to stir at 50 °C overnight, **7** was consumed. The conditions in eq 2 were further validated by successfully performing the coupling on a 1 kg scale.



The utility of this coupling process was extended to other systems (Table 2). Coupling of arylamides and alkylamides to bromoethoxyfuranone occurred readily (entries 1 and 2), as well as the coupling of carbamates (entry 3). The reaction also worked well for the coupling of amides, carbamates, and heterocyclic amides to β-bromoacrylates (entries 4 and

Table 2. Pd-Catalyzed Coupling of Amides and Carbamates to β-Bromoacrylates, β-Bromoacrylamides, and **7**[a]

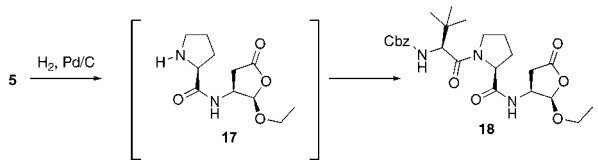
entry	amide/ carbamate	bromide	product (yield)
1			 **8**, 92%
2			 **9**, 86%
3			 **10**, 46%
4			 **11**, 92%
5			 **12**, 76%
6		 **16**	 **13**, 84%
7		 **16**	 **14**, 80%
8		 **16**	 **15**, 45%

[a] Conditions: 1.1 equiv of bromide, 1 mol % of $Pd(OAc)_2$, 1.5 mol % of Xantphos, K_2CO_3 (2 equiv), water (3 equiv), toluene, 60 °C, 3−3.5 h.

5, respectively) and to β-bromoacrylamides (entries 6−8). The reactions were comparable in rates. The acrylate products were susceptible to isomerization if allowed to remain at elevated temperatures for extended periods after reaction completion.

Having demonstrated an efficient coupling process, the next task required isolation of the single diastereomer **5** (from its 1:1 mixture with ethoxy epimer *epi*-**5**) and stereoselective reduction of the double bond to give **17** (Scheme 3).

Scheme 3. Stereoselective Hydrogenation of **5** and Coupling to Z-Tle-OH



Gratifyingly, after a simple aqueous workup of the crude reaction mixture and concentration, **5** fractionally crystallized from the reaction mixture in 37% isolated yield as a 93:7 mixture of diastereomers. After recrystallization from toluene (90% recovery), diastereomerically pure **5** was isolated as a white solid. Subsequent hydrogenation effected stereoselective reduction of the double bond and concomitant removal of the Cbz protecting group to give **17**. Compound **17** was transformed to VX-765 via coupling with Z-Tle-OH (to give **18**), removal of the Cbz protecting grouping, and coupling to benzoic acid **1**.

In conclusion, we have developed a novel Pd-catalyzed coupling process for the conversion of β-bromoenoates to β-amidoenoates within the context of a target-oriented synthesis of the key intermediate of ICE inhibitor VX-765. The process demonstrates the ability to perform the coupling under conditions mild enough to allow efficient conversion of base-sensitive bromides. Additionally, the methodology was shown to be successful for the coupling of carbamates and a range of amides to β-bromoacrylates and β-bromoacrylamides.

Acknowledgment. G.J.T. thanks Prof. Brian Stoltz for helpful discussions.

Supporting Information Available: Characterization data, NMR spectra, detailed experimental procedures, and structures of phosphine ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702532H