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Simple Approach to β-Lactam Derivatives from *N*-Acylimidazoles

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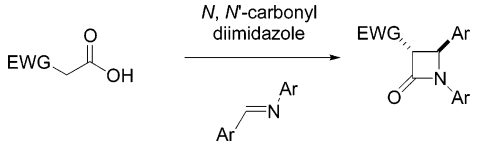

Reaction of *N*-acylimidazoles possessing an electron-withdrawing group in the α position with diarylimines produces β-lactams in high yields.

Substituted β-lactams attract considerable research interest because of their biological activity[1] and their ability to serve as versatile building blocks in synthesis.[2] Building β-lactam rings is a crucial step in synthesis of new β-lactam antibiotics,[3] and development of new preparative approaches toward β-lactam cycles is highly important.

Preparation of β-lactams through cycloaddition of ketenes to imines allows convergent syntheses of substituted β-lactams.[4] Although a number of methods for preparation of ketenes have been introduced,[5] reaction of acyl halides with tertiary amines remains the most preparatively useful approach because of the availability of starting material. However, in a number of cases, application of acyl halides produces inadequate results. For example, [2 + 2] cycloaddition to imines with ketenes that were generated from acyl halides possessing strong electron-withdrawing groups (EWG) such as carbonyl, phosphoryl, or sulfonyl produces low yields of corresponding β-lactams.[6]

For preparation of EWG-substituted β-lactams a number of useful alternatives to [2 + 2] cycloaddition of ketenes to imines have been proposed. 3-Alkoxycarbonyl-, 3-phosphoryl-, and 3-sulfonyl-substituted β-lactams have been obtained by free radical cyclization of enamides,[7] acid-catalyzed rearrangement of spiro[cyclopropane-1,5′-isooxazolidines],[8] and through ruthenium[9] and rhodium[10] catalyzed intramolecular carbene insertion of tertiary 2-diazocarboxamides. However, these methods are based on multistep protocols and are problematic for substrates bearing functionalities sensitive to carbenes or oxidants. The regioselectivity or stereoselectivity of ring closure in many cases is unacceptably low.[10a,b,h,j]

Recently, a rhodium-catalyzed Wolf rearrangement of thioesters was used for preparation of 3-alkoxycarbonyl β-lactams.[11] However, this method necessitates an additional desulfurization step and provides an ambiguous stereochemical outcome.

We have published a method for generation of ketenes through reaction of α-EWG substituted carboxylic acids with carbodiimides.[12,13] Ketenes of type **2** generated in situ by this reaction were found to react with sterically hindered alcohols, allowing their acylation in the presence of phenol or thiol functionalities (Scheme 1).[14] In the absence of alcohols, trapping of ethoxycarbonylketene in situ with a second equivalent of a carbodiimide was found to produce oxazines through [4 + 2] cycloaddition.

On the basis of the efficient trapping of the ketene intermediates with alcohols and carbodiimides, we expected that similar trapping with imines could serve as an attractive method for preparation of β-lactams that are difficult to synthesize by conventional methods. Our initial approach involved reactions of carboxylic acids of type **1** with 1 equiv of dicyclohexylcarbodiimide (DCC) in the presence of an excess of *N*-benzylideneaniline (Scheme 1).

In contrast to our expectations, no traces of β-lactams of type **4** have been observed. Carboxylic acids of type **1** produced a complex mixture of products. These results can be attributed to fast reactions of corresponding ketenes with other nucleophiles that proceed faster than the relatively slow [2 + 2] cycloaddition.

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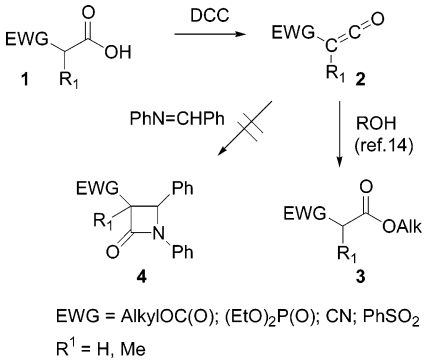
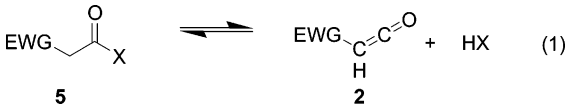
SCHEME 1



The initial failure to get cycloaddition products prompted us to examine an alternative way to generate ketenes that would exclude concomitantly generated nucleophiles that might result in reactions competing with [2+2] cycloadditions. Although generation of ketenes from carboxylic acids of type **1** can be achieved with a number of coupling reagents,[14] each of them should produce an equimolar amount of a nucleophile that will compete with the relatively slow [2 + 2] cycloaddition with imines.

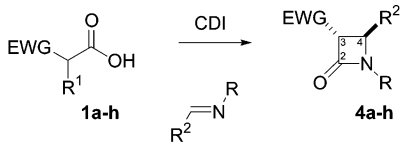
Consequently, we adopted another strategy to generate ketenes of type **2**. Instead of attempting to trap ketene intermediates that are quantitatively produced through treatments of carboxylic acids of type **1** with carbodiimides, it might be possible to generate a small concentration of ketenes of type **2** through a reversible dissociation of derivatives of type **5** (eq 1). In this case the equilibrium concentration of ketenes of type **2** would be small but constant, thus allowing their [2 + 2] cycloaddition with an imine.



This would be possible if carboxylic derivatives of type **5** possess a relatively weak X-CO bond that would provide a sizable equilibrium concentration of ketene of type **2**, and there is a possibility for fast elimination of HX in the absence of basic catalysts (i.e., tertiary amines) that can produce undesirable zwitter-ionic adducts.[15] Both of these requirements can be achieved if imidazole is employed as the leaving group.

The practice of using 1,1-carbonyldiimidazole (CDI) as coupling reagent is extensive. It has been used for preparation of esters, amides, thioesters, and other carboxylic acid derivatives.[16] To the best of our knowledge, there are no examples of use of *N*-acylimidazoles for generation of ketenes. The only relevant, similar examples involve generation of ethyl ketenes from *N*-acylbenzotriazoles by thermolysis[17] or treatment with NaH.[18] These harsh conditions are understandable, since the low basicity of imidazole is not sufficient for producing ketenes from

SCHEME 2



	EWG	R	R^1	R^2	Yield, %
a	EtOC(O)-	Ph	H	Ph	98
b	Ph–S(O)-	Ph	H	Ph	97
c	$PhSO_2$-	Ph	H	Ph	96
d	$(EtO)_2P(O)$-	Ph	H	Ph	99
e	$(EtO)_2P(O)$-	Ph	H	4-Br-C_6H_4	98
f	$(EtO)_2P(O)$-	Ph	H	4-CN-C_6H_4	94
g	$(EtO)_2P(O)$-	Ph	H	4-Cl-C_6H_4	98
h	EtOC(O)-	Ph	Me	Ph	0
i	NC-	Ph	H	Ph	0
k	tBuS(O)-	Ph	H	Ph	0
l	MeS(O)-	Ph	H	Ph	0
m	$(EtO)_2P(O)$-	$Ph(CH_2)_2$-	H	Et	0
n	$(EtO)_2P(O)$-	Ph	H	CH_2CO_2Et	0

N-acylimidazoles through E1cb elimination reaction. The situation is different for *N*-acylimidazoles that possess highly acidic α hydrogens that can be abstracted with relatively weak bases such as imidazole itself.[19]

In line with our predictions, treatment of carboxylic acids **1a**−**g** with 1.1 equiv of CDI followed by reaction with imines produced the corresponding *β*-lactams **4a**−**g** with essentially quantitative yield (Scheme 2). According to ^{1}H NMR data all *β*-lactams **4a**−**g** possessed *trans* stereochemistry as evidenced by coupling constants of endocyclic protons (2.2−2.9 Hz).[20] Exclusive *trans* stereoselectivity for these compounds is most likely related to easy epimerization of the highly acidic α proton that produced the much more thermodynamically stable *trans* isomer.

In addition to known *β*-lactams **4a,c,d**, similar products were obtained for phenylsulfinylacetic acid **1b**. Steric induction by the chiral sulfoxide function was found to be moderate, thus providing a 2.5:1 mixture of diastereomers. Despite the high yield of *β*-lactams **1b**, both *tert*-butyl- and methylsulfinylacetic acids failed to provide even a trace amount of *β*-lactams. Most probably, the lack of reactivity of alkylsulfinylacetic acids is due to the lower acidity[21] of the α protons that precludes E1cb elimination of imidazole in the corresponding *N*-acylimidazoles and formation of ketenes of type **2**.

Carboxylic acids **1h** and **1i** possessing sufficiently acidic α protons also failed to provide *β*-lactams. Lack of reactivity of monoethyl 2-methyl is most probably related to the substantially

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lower reactivity of disubstituted versus monosubstituted ketenes.[22] Lack of reactivity of the imidazolide of cyanoacetic acid can be attributed to the lower stability of the corresponding ketene,[23] which can result in its very low equilibrium concentration in the reaction mixture.

Attempts to conduct similar [2 + 2] cycloadditions using carboxylic acids of type **1** and substituted alkenes such as ethoxyethylene, cyclopentadiene, or 2,3-dihydrofurane did not provide any trace of the corresponding cyclobutanes. Similarly, no cycloaddition was observed with substituted alkynes such as phenylacetylene. Reactions with other imines such as *N*-propylidene-2-phenylethylamine and ethyl *N*-benzylideneglycinate did not provide β-lactams, most probably because of the low stability of the imines in the presence of imidazole, which is an unavoidable component of the reaction mixture.

In conclusion, we have demonstrated that *N*-acylimidazoles possessing an electron-withdrawing group at the α position are capable of producing β-lactams in high yield. The observed results are compatible with a reaction mechanism involving reversible generation of low concentrations of the corresponding ketenes followed by their trapping with substituted imines.

Experimental Section

General Procedure for Preparation of β-Lactams (4a−g). A solution of acid of type **1** (1 mmol) and CDI (178 mg, 1.10 mmol) in dichloromethane (1 mL) was stirred at 25 °C for 1 h. To the reaction mixture was added 1.0 mL of a corresponding imine in solution (1 M solution, CH_2Cl_2). The reaction mixture was stirred for 1 h, filtered through Celite, and evaporated. The residue was purified by flash chromatography (neat chloroform) to afford title compounds.

***trans*-3-Ethoxycarbonyl-1,4-diphenyl-azetidin-2-one (4a).**[10a] Colorless oil, 98%; IR ($CDCl_3$) 3019, 1762, 1731, 1215, 757 cm^{-1}; ^1H NMR (300 MHz) 1.23 (t, $J = 7.0$ Hz, 3H), 3.88 (d, $J = 2.4$ Hz, 1H), 4.19 (q, $J = 7.3$ Hz, 2H), 5.25 (d, $J = 2.4$ Hz, 1H), 6.95−7.30 (m, 10H); ^{13}C NMR (100.62 MHz) 14.15, 57.25, 62.12, 63.58, 117.18, 124.41, 126.20, 127.08, 129.05, 129.12, 136.35, 137.20, 1259.27, 166.30.

***trans*-3-Benzenesulfinyl-1,4-diphenyl-azetidin-2-ones (4b).** White amorphous solid mixture of diastereomers in 2.5:1 ratio, mp 140−141 °C (major isomer), 97%; IR ($CDCl_3$) 3018, 1757, 1500, 1215, 757 cm^{-1}; ^1H NMR (300 MHz) 4.08 (d, $J = 2.4$ Hz, 1H, minor stereoisomer), 4.27 (d, $J = 2.4$ Hz, 1H, major stereoisomer), 5.28 (d, $J = 2.4$ Hz, 1H, major stereoisomer), 5.41 (d, $J = 2.4$ Hz, 1H, minor stereoisomer), 6.82−7.77 (m, 15H [major] + 15H [minor]); ^{13}C NMR (100.62 MHz) 56.2, 76.4, 117.1, 124.5, 124.9, 126.2, 128.9, 129.1, 129.1, 129.3, 131.9, 135.5, 136.5, 139.0, 157.3. Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60, H, 4.93, N, 4.03. Found: C, 72.35, H, 5.05, N, 4.00.

***trans*-3-Benzenesulfonyl-1,4-diphenyl-azetidin-2-one (4c).** White solid, mp 156−157 °C, 96%; IR ($CDCl_3$) 3019, 1764, 1215, 757 cm^{-1}; ^1H NMR (300 MHz) 4.36 (s, 1H), 5.45 (s, 1H), 6.97−7.80 (m, 15H); ^{13}C NMR (100.62 MHz) 56.02, 77.5, 117.2, 124.9, 125.9, 128.7, 129.1, 129.2, 129.3, 134.6, 134.6, 136.5, 137.6, 155.5. Anal. Calcd for $C_{21}H_{17}NO_3S$: C, 69.40, H, 4.71, N, 3.85. Found: C, 69.00, H, 4.69, N, 3.80.

***trans*-3-Diethoxyphosphoryl-1,4-diphenyl-azetidin-2-one (4d).**[6a] Pale yellow crystals, mp 81−83 °C, 99%; IR ($CDCl_3$) 3018, 1756, 1215, 757 cm^{-1}; ^1H NMR (300 MHz) 1.31 (dt, $J_1 = 6.9$ Hz, $J_2 = 5.4$ Hz, 6H), 3.50 (dd, $J_1 = 15.4$ Hz, $J_2 = 2.9$ Hz, 1H), 4.19 (dq, $J_1 = 7.7$ Hz, $J_2 = 7.3$ Hz, 4H), 5.18 (dd, $J_1 = 15.4$ Hz, $J_2 = 2.9$ Hz, 1H), 7.03−7.39 (m, 10H); ^{13}C NMR (100.62 MHz) 16.1, 16.2, 55.5, 55.5, 56.2, 57.7, 62.5, 62.6, 62.8, 62.9, 116.7, 124.0, 125.6, 128.7, 128.8, 129.0, 136.2, 136.3, 137.0, 137.0, 158.6, 158.7. Anal. Calcd for $C_{19}H_{22}NO_4P$: C, 63.50, H, 6.17, N, 3.90. Found: C, 63.21, H, 6.12, N, 3.58.

***trans*-3-Diethoxyphosphoryl-1-phenyl-4-(4-bromophenyl)azetidin-2-one (4e).** White crystals, mp 75−76 °C, 98%; IR ($CDCl_3$) 3018, 1758, 1215, 754 cm^{-1}; ^1H NMR (300 MHz) 1.28 (dt, $J_1 = 4.4$ Hz, $J_2 = 4.0$ Hz, 6H), 3.44 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.9$ Hz, 1H), 4.15 (dq, $J_1 = 7.7$ Hz, $J_2 = 7.3$ Hz, 4H), 5.13 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.9$ Hz, 1H), 6.97−7.30 (m, 9H); ^{13}C NMR (100.62 MHz) 16.3, 16.4, 55.1, 55.1, 56.1, 58.1, 62.7, 62.8, 63.1, 63.2, 116.8, 124.4, 129.1, 129.3, 134.7, 134.9, 135.0, 136.9, 137.0, 158.6, 158.7; HRMS calcd for $C_{19}H_{21}BrNO_4PNa^+$ 460.0284, found 460.0268.

***trans*-3-Diethoxyphosphoryl-1-phenyl-4-(4-cyanophenyl)azetidin-2-one (4f).** Pale yellow crystals, mp 83−84 °C, 94%; IR ($CDCl_3$) 3019, 2400, 2233, 1761, 1215, 754 cm^{-1}; ^1H NMR (300 MHz) 1.28 (dt, $J_1 = 6.9$ Hz, $J_2 = 2.2$ Hz, 6H), 3.44 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.5$ Hz, 1H), 4.15 (dq, $J_1 = 7.7$ Hz, $J_2 = 7.3$ Hz, 4H), 5.21 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.5$ Hz, 1H), 7.01−7.24 (m, 5H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (100.62 MHz) 16.4, 16.5, 55.27, 55.19, 56.4, 57.8, 63.0, 63.1, 63.4, 63.5, 113.0, 116.8, 118.1, 124.8, 126.7, 129.3, 133.2, 136.9, 136.9, 142.0, 142.0, 158.3, 158.4; HRMS calcd for $C_{20}H_{21}N_2O_4PH^+$ 385.1313, found 385.1317.

***trans*-3-Diethoxyphosphoryl-1-phenyl-4-(4-chlorophenyl)azetidin-2-one (4g).** White crystals, mp 93−94 °C, 98%; IR ($CDCl_3$) 3018, 1758, 1215, 754 cm^{-1}; ^1H NMR (300 MHz) 1.28 (dt, $J_1 = 4.4$ Hz, $J_2 = 4.4$ Hz, 6H), 3.44 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.9$ Hz, 1H), 4.15 (dq, $J_1 = 7.7$ Hz, $J_2 = 7.3$ Hz, 4H), 5.13 (dd, $J_1 = 15.8$ Hz, $J_2 = 2.9$ Hz, 1H), 6.98−7.30 (m, 9H); ^{13}C NMR (100.62 MHz) 16.36, 16.44, 55.21, 55.23, 56.1, 58.1, 62.8, 62.9, 63.2, 63.3, 116.9, 122.9, 124.5, 127.5, 129.1, 132.5, 135.7, 137.00, 137.03, 158.6, 158.7. Anal. Calcd for $C_{19}H_{21}ClNO_4P$: C, 57.95, H, 5.37, N, 3.56. Found: C, 57.66, H, 5.46, N, 3.43.

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Supporting Information Available: Complete experimental details and copies of ^1H and ^{13}C NMR spectra of products **4a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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