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Cycloaddition Reactions of Imines with 3-Thiosuccinic Anhydrides: Synthesis of the Tricyclic Core of Martinellic Acid

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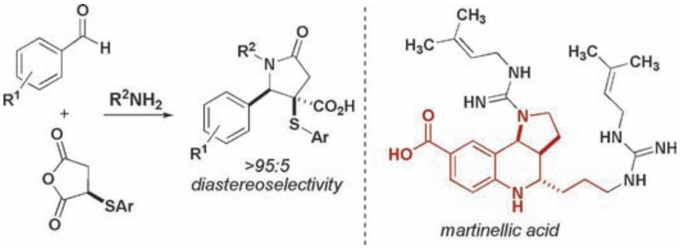
ABSTRACT



Arylthio-substituted succinic anhydrides undergo cycloaddition reactions with imines to produce γ-lactams in high yield and with high diastereoselectivity. The origin of the selectivity is proposed to result from anion−π repulsion in the transition state. The utility of this technique is demonstrated in a synthesis of the carbon framework common to the alkaloids martinellic acid and martinelline in five steps.

The diastereoselective synthesis of heterocyclic compounds is important for the discovery of biologically relevant compounds in drug discovery, chemical biology, and the synthesis of natural products.[1] γ-Lactams are an important class of unsaturated heterocycles featured in natural products and drug candidates.[2] The reaction of imines with succinic anhydrides represents an efficient, one-step synthesis of these compounds. The isolated[3] reports of lactam syntheses using this reaction suggest that the substrate scope is quite narrow (Figure 1, eqs 1 and 2). A recent report from our laboratory[4] details the importance of electronic factors on the reactivity of the anhydride component (Figure 1, eq 3). In this report, we exploit this effect to establish the reaction of imines with succinic anhydrides as a general method for γ-lactam synthesis.

Our observations on how substituent effects influence the rate of the reaction between aryl-substituted anhydrides and imines prompted us to examine heteroatom-substituted anhydrides. An inspection of substituted acetophenone acidity data[5] suggests that oxygen, nitrogen, and sulfur substituents confer various levels of stabilization to the conjugate base (Figure 2). On the basis of this trend, we hypothesized that heteroatom-substituted anhydrides would facilitate the imine−anhydride cycloaddition.

We tested this hypothesis by employing a series of heteroatom-substituted anhydrides[6] in addition reactions with imine **15**. Anhydrides **16−20** were allowed to react with the *N*-benzyl imine of *ortho*-bromobenzaldehyde (**15**) using conditions optimized for phenylsuccinic anhydride.[4] The reactions of nitrogen- and oxygen-substituted anhydrides

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(1) Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2125−2126 and references therein.

(2) (a) Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245−2303. (b) Smith, M. B. *Sci. Synth.* **2005**, *21*, 647−711.

(3) (a) Castagnoli, N., Jr., *J. Org. Chem.* **1969**, *34*, 3187−3189. (b) Castagnoli, N., Jr.; Cushman, M. *J. Org. Chem.* **1971**, *36*, 3404−3406. (c) Cushman, M.; Castagnoli, N., Jr., *J. Org. Chem.* **1972**, *37*, 1268−1271. (d) Dallacker, F.; Jouck, W. *Chem.-Ztg.* **1985**, *109*, 82−84. (e) Cushman, M.; Madaj, E. J. *J. Org. Chem.* **1987**, *52*, 907−915.

(4) Masse, C. E.; Ng, P. Y.; Fukase, Y.; Sanchez-Rosello, M.; Shaw, J. T. *J. Comb. Chem.* **2006**, *8*, 293−296.

(5) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463. (b) Bordwell, F. G.; Lynch, T. Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558−7562.

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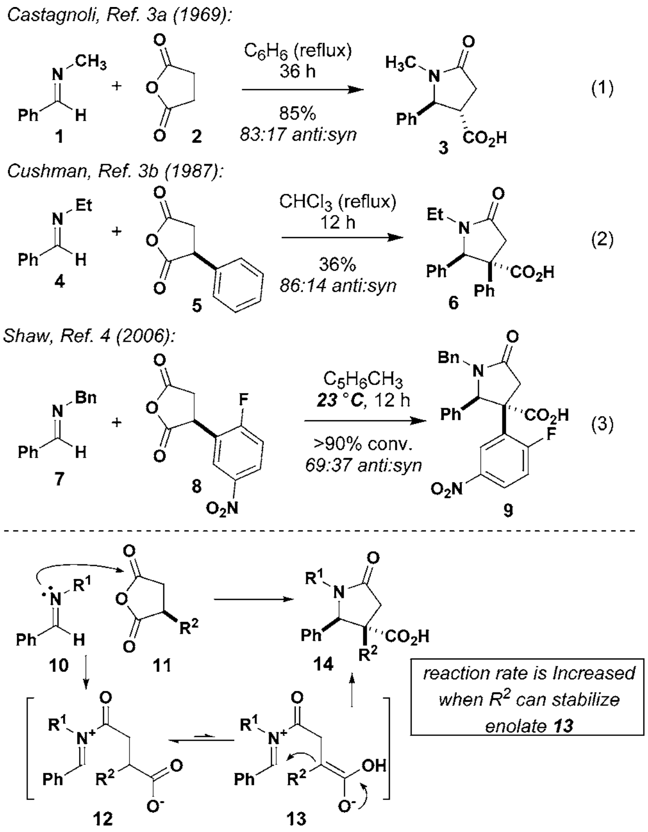
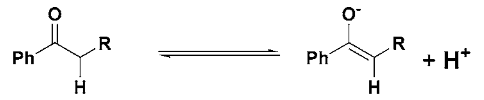


Figure 1. Reactions of imines with succinic anhydrides: increasing the enolate stabilization facilitates the reaction.

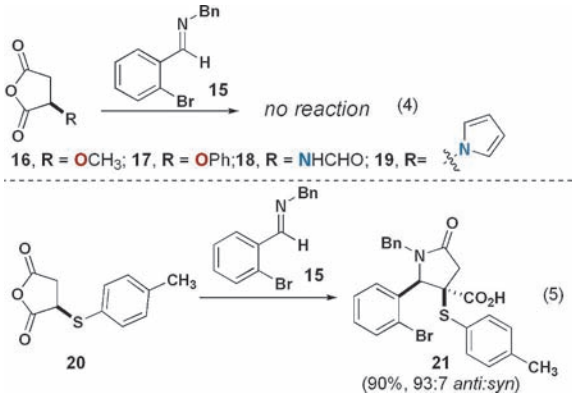


R	H	OCH_3	OPh	NPh_2	Ph	SPh
pK_a	24.7	22.9	21.1	20.3	17.7	16.9

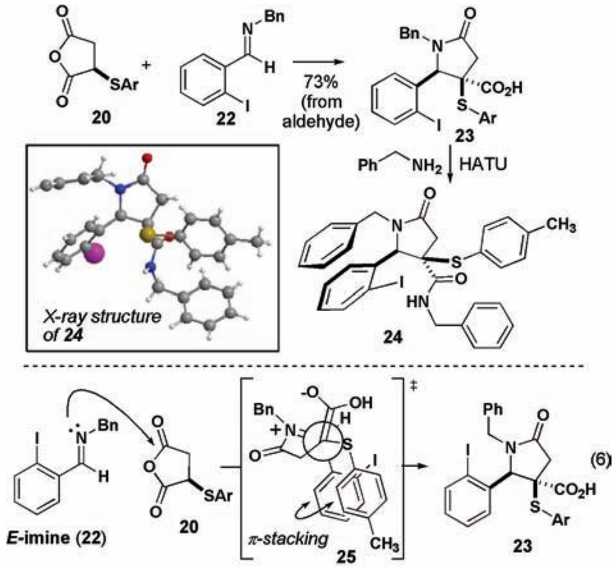
Figure 2. Effect of heteroatom substitution on enolate stability.

showed either no conversion or the formation of unidentified byproducts (eq 4). In contrast, sulfur-substituted anhydride **20** afforded the desired lactam product **21** in high yields and with the highest diastereoselectivity yet observed in this reaction (eq 5).

The reaction of imines with anhydride **20** preferentially leads to the anti diastereomer, as found with phenylsuccinic anhydride. Iodo-substituted acid **23** was prepared in analogy to **21** and converted to amide **24**, which yielded a crystalline sample that was analyzed using X-ray crystallography (Scheme 1). The observed stereochemical outcome is consistent with a favorable π-stacking interaction in the transition state **25** between the two aromatic rings (eq 6).



Scheme 1. Synthesis of **24** and Establishment of the Relative Stereochemistry by X-ray Crystallography



The importance of π-stacking was evaluated by testing the reactivity of a thio*alkyl*-substituted succinic anhydride. *N*-Butylthio-substituted anhydride **26** was allowed to react with imine **15** under the standard conditions, and a nearly identical selectivity was observed for the anti diastereomer.[7] This result demonstrates that steric and/or electrostatic factors, rather than a π-stacking interaction, are mainly responsible for the selectivity observed in this reaction.

The observed selectivity in the reactions of thio-substituted anhydrides with imines can be rationalized by invoking a repulsive interaction between the negative charge of the

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(6) Anhydride **18** was purchased from Sigma-Aldrich. Anhydrides **16**, **17**, **19**, and **20** were synthesized by reported methods, with minor modifications (see Supporting Information). **16**: (a) Barton, D. H. R.; Benechie, M.; Khuong-Huu, F., Potier, P.; Reyna-Pinedo, V. *Tetrahedron Lett.* **1982**, *23*, 651−654. **17**: (b) Sheppard, G. S. *Synlett* **1999**, 1207−1210. **19**: (c) Box, S. J.; Corbett, D. F. *Tetrahedron Lett.* **1981**, *22*, 3293−3296. (d) D'Silva, C.; Walker, D. A. *J. Org. Chem.* **1998**, *63*, 6715−6718. **20**: (e) Zienty, F. B.; Vineyard, B. D.; Schleppnik, A. A. *J. Org. Chem.* **1962**, *27*, 3140−3146.

[7] The relative configuration of this compound was proven by conversion to the *p*-methoxyphenethyl amide and NOE spectroscopy. See Supporting Information.

carboxylate and the aromatic ring of the imine in the transition state (Figure 3). Although the attractive interactions of cations with π-systems have been extensively studied,[8] analogous studies of anion−π interactions are less common. Deya has described the attraction of anions to electron-*deficient* arenes in detail.[9] This interaction has also been used to explain the bonding of aromatic heterocycles in macromolecular structures.[10] Although one would assume that the interaction of an anion with an electron-*rich* arene would be repulsive, this phenomenon has not been well-documented. One study of Lewis acids and bases interacting with arenes concludes that ammonia experiences an attractive interaction with hexafluoro-benzene and a repulsive interaction with the π-face of benzene (Figure 4).[11] Although the repulsion of the carboxylate and the aryl ring in the transition state of the imine−anhydride reaction (Figure 3) is consistent with the observed stereochemistry, further experimentation will bolster this argument.[12] To our knowledge, this is the first instance in which anion−π repulsion has been invoked in a transition state to explain the stereochemical outcome of a reaction.

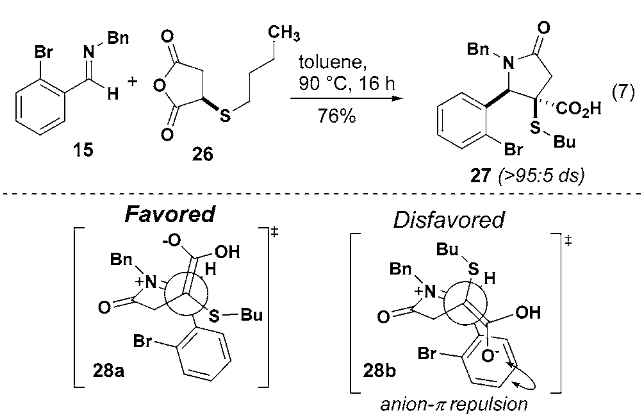


Figure 3. Reaction of **15** with thiobutyl succinic anhydride **26** (eq 7). The stereoselectivity is explained by anion-π repulsion in transition state **28b**.

We explored the scope of this reaction with a variety of substituted imines (Table 1). Regardless of the N-substitution or the presence or absence of ortho substituents on the aromatic ring, good yields and excellent diastereoselectivities were observed for the reactions of imines with anhydride **20**.

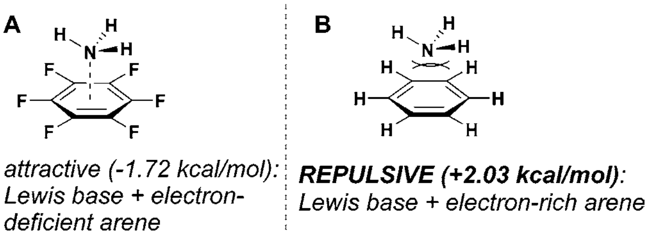
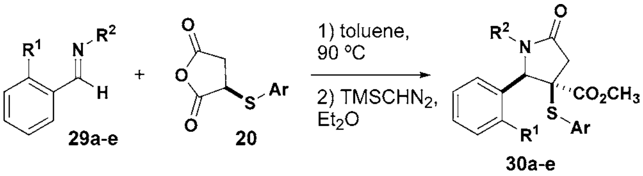


Figure 4. Interaction between a Lewis base (ammonia) which has been calculated to be attractive (**A**) when the arene is electron deficient and to be repulsive (**B**) when the arene is electron rich. Interaction energy calculated at the MP2/aug-ccpVDZ//B3LYP/6-311G(d) level.[11]

To demonstrate the utility of this technique, a cycloaddition/reduction sequence was used to prepare the tricyclic core shared by martinellic acid and martinelline in a short synthetic sequence. These two natural products were isolated from the tropical plant *Martinella iquitosensis.*[13] These two compounds share a common tricyclic core and their “deceptively simple”[14d] structures have attracted much synthetic effort.[14] Commercially available aldehyde **31** was treated with benzylamine, followed by anhydride **20**, to produce lactam

Table 1. Reaction of Anhydride **20** with Various Imines



entry	R¹	R²	yield[a]	diastereoselectivity[b]
1	NO_2	Bn	80%	>95:5
2	N_3	Bn	85%	>95:5
3	H	CH_2(^{i}Pr)	62%	>95:5
4	H	^{i}Pr	58%	>95:5
5	H	PMB[c]	76%	>95:5

[a] Yield over two steps from aldehyde starting material. [b] Determined by ^{1}H NMR spectroscopy. [c] PMB = *p*-methoxybenzyl.

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(8) Dougherty, D. A. *Science* **1996**, *271*, 163−168.

(9) (a) Quinonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389−3392. (b) Garau, C.; Quinonero, D.; Frontera, A.; Ballester, P.; Costa, A.; Deya, P. M. *New J. Chem.* **2003**, *27*, 211−214. (c) Garau, C.; Frontera, A.; Quinonero, D.; Ballester, P.; Costa, A.; Deya, P. M. *Chem. Phys. Lett.* **2004**, *399*, 220−225.

(10) (a) Schottel, B. L.; Chifotides, H. T.; Shatruk, M.; Chouai, A.; Perez, L. M.; Bacsa, J.; Dunbar, K. R. *J. Am. Chem. Soc.* **2006**, *128*, 5895−5912.

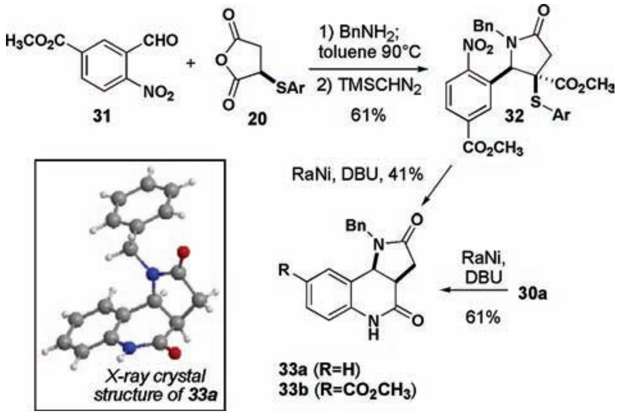
(11) Kawahara, S.-i.; Tsuzuki, S.; Uchimaru, T. *Chem.−Eur. J.* **2005**, *11*, 4458−4464.

(12) We have attempted a reaction between the benzylimine of pentafluorobenzaldehyde and anhydride **20**, which was expected to give the lactam product with reduced diastereoselectivity. No conversion was observed, possibly due to reduced basicity of the imine nitrogen.

(13) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682−6685.

(14) Enantioselective synthesis of martinellic acid: (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189−2191. Syntheses of racemic martinellic acid and martinelline: (b) Snider, B. B.; Ahn, Y.; O’Hare, S. M. *Org. Lett.* **2001**, *3*, 4217−4220. (c) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405−9409. (d) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916. Syntheses of the tricyclic core: (e) He, Y.; Moningka, R.; Lovely, C. J. *Tetrahedron Lett.* **2005**, *46*, 1251−1254. (f) Takeda, Y.; Nakabayashi, T.; Shirai, A.; Fukumoto, D.; Kiguchi, T.; Naito, T. *Tetrahedron Lett.* **2004**, *45*, 3481−3484. (g) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417−6419. (h) Hara, O.; Sugimoto, K.; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625−1627. (i) Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 9381−9390. (j) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N.; Walker, A. D. *Tetrahedron* **2006**, *62*, 3977−3984.

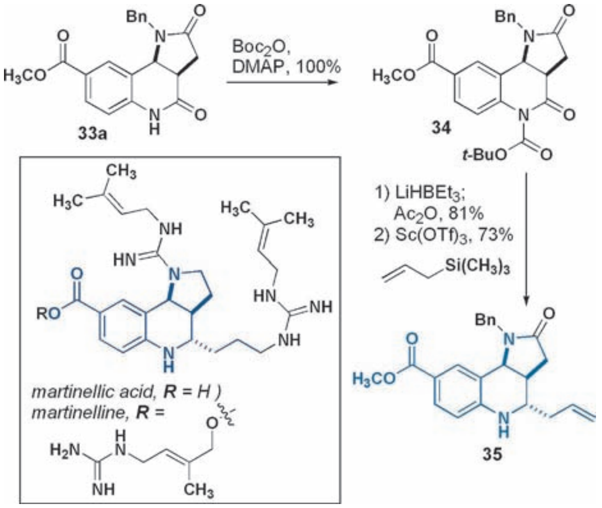
Scheme 2. Imine−Anhydride Cycloaddition and Reductive Desulfurization/Cyclization



32 in 61% yield and >95:5 diastereoselectivity (Scheme 2). Treatment of this compound with Raney nickel effected reductive cleavage of the arylthio group as well as reduction of the nitro group to the corresponding aniline, which underwent partial cyclization with the ester to form tricyclic lactam **33b**. The resultant mixture of cyclized and uncyclized material was treated with DBU to complete cyclization in 41% yield. In a model study, a similar sequence was used to convert **30a** into **33a**, for which we obtained crystals suitable for X-ray crystallography, confirming the expected *cis* ring fusion. Thus, the complete core connectivity of martinellic acid is produced in two linear steps, the shortest preparation of this intermediate to date.

Tricyclic core **33b** was converted to the complete carbon framework of martinellic acid and martinelline in three steps (Scheme 3). Attachment of a Boc group to the amine produced imide **34**. This compound was chemoselectively reduced to the *N*,*O*-acetal using $\mathrm{LIHBEt_3}$ and acetic anhydride.[15] Formation of an *N*-acyliminium ion using $\mathrm{Sc(OTf)_3}$ and trapping with allyltrimethylsilane were accompanied by simultaneous loss of the *N*-Boc group in 73% overall yield. A single diastereomer of tricyclic lactam **35** was observed, and the relative configuration was assigned with NOE spectroscopy.[16] Although a related approach using an iminium ion precursor was attempted by Lovely, it was unsuccessful.[14e] We attribute the higher conversion and lack of byproduct formation in our case to the increased reactivity of the *N*-acyl iminium ion intermediate.[17]

Scheme 3. Completion of the Tricyclic Core of Martinellic Acid and Martinelline



In summary, we report a diastereoselective cycloaddition reaction that is used to produce 1,4,5-trisubstituted γ-lactams. The two-step sequence is synthetically equivalent to the direct reaction of succinic anhydride with imines but more efficient and with higher diastereoselectivity. We have used this process to synthesize the tricyclic core of martinellic acid and martinelline, and we are currently executing a short, enantioselective synthesis of these natural products.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds, as well as X-ray crystallographic data for **24** and **33a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] (a) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663−1667. (b) Pilli, R. A.; Robello, L. G. *Synlett* **2005**, 2297−2300.

[16] See Supporting Information.

[17] Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.