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Diastereoselective Synthesis of γ-Lactams by a One-Pot, Four-Component Reaction

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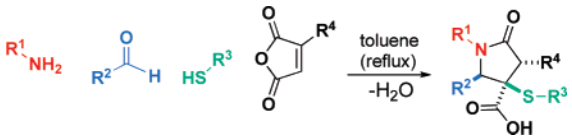
ABSTRACT



A new one-pot, four-component reaction (4CR) between amines, maleic anhydrides, aldehydes, and thiols has been discovered to form tetra- and pentasubstituted γ-lactams with high diastereoselectivity. Each component is independently variable and employed in equivalent stoichiometry, producing only water as a byproduct.

Multicomponent reactions (MCRs) are an important class of chemical transformations for the efficient synthesis of natural products and screening compounds for the discovery of biological probes and drugs.[1] The Hantsch[2] and Biginelli[3] reactions are important for the synthesis of heterocycles, whereas the Passerini,[4] Ugi,[5] and Petasis[6] MCRs are useful methods for preparing α-hydroxy and α-amino carboxylic acid derivatives.[7] To date, few four-component reactions (4CRs) have been reported to form multiple stereogenic centers with a high level of diastereoselection.[8] Herein, we disclose the first 4CR for the diastereoselective synthesis of γ-lactams wherein either two or three stereocenters are formed with high selectivity.

Our recent discovery of the formal cycloaddition of imines to 2-arylthiosuccinic anhydrides[9] prompted us to probe the mechanism of this reaction. Of particular interest was the high regioselectivity in the attack of the imine on the anhydride. The opening of 2-substituted succinic anhydrides by amine nucleophiles is known to be unselective,[10] presumably due to competing steric and stereoelectronic effects.[11] On the basis of the high regioselectivity required for the yields that we observe, we reasoned that the reactions of anhydride **2** with imines must be reversible (Scheme 1) and that only the isomer with the α-thioaryl substituent (**5a**) was sufficiently enolizable to proceed on to the observed product **6**.

The reversibility of imine attack on anhydride **2** was tested using alternate conditions to access intermediates **3** and **5a**. The reaction of benzylamine with anhydride **2** produces the

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(1) (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321−3329. (b) Zhu, J., Bienayme, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005; p 468.

(2) (a) Hantzsch, A. *Liebigs Ann. Chem.* **1882**, *215*, 1−82. (b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957−4980.

(3) (a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962−2967. (b) Kappe, C. O.; Stadler, A. *Org. React. (NY)* **2004**, *63*, 1−116.

(4) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181−189. (b) Banfi, L.; Riva, R. *Org. React. (NY)* **2005**, *65*, 1−140.

(5) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbruckner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89.

(6) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583−586. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445−446.

(7) (a) For an example of a five-component reaction in which hexasubstituted benzenes are produced in a one-pot sequential process, see: Janvier, P.; Bienayme, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4291−4294. (b) For an example of a seven-component reaction, see: Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **1993**, *32*, 563−564.

(8) For direct comparison, we are limiting our description of 3CRs and 4CRs to those in which all of the components can be independently varied. The Hantzsch, Biginelli, Passerini, and Petasis 3CRs and the Ugi 4CR are all examples of MCRs in which each component can, to a certain extent, be varied independently. For a comprehensive discussion of many MCRs discovered to date, see ref 1.

(9) Ng, P. Y.; Masse, C. E.; Shaw, J. T. *Org. Lett.* **2006**, *8*, 3999−4002.

(10) Stephani, R.; Cesare, V.; Sadarangani, I.; Lengyel, I. *Synthesis* **2002**, 47−52.

(11) (a) Rosenfield, R. E., Jr.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2176−2189. (b) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192−1198.

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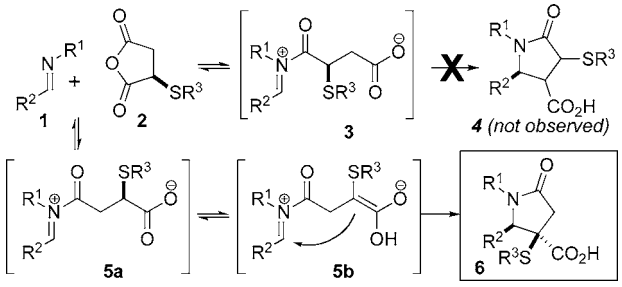
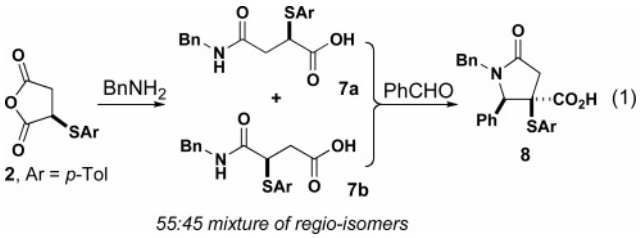
Scheme 1. Reversibility of the Imine−Anhydride Reaction

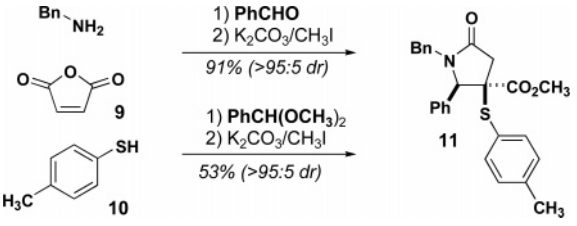


hemi-acid products **7a** and **7b** in a 55:45 ratio (eq 1). The mixture of amides **7a** and **7b** was allowed to react with benzaldehyde in refluxing toluene under dehydrating conditions. Nearly quantitative conversion to lactam **8** was observed. In addition, **7a** and **7b** were prepared, separated, and carried on to **8** in independent reactions.[12] These results are consistent with the intermediacy of *N*-acyl iminium ion **5a** in the formation of lactam **8**. A three-component reaction (3CR) whereby benzylamine, anhydride **2**, and benzaldehyde were combined in a single operation also produced lactam **8** in high yield.



The demonstration that amides **7a** and **7b** produce the same product as the imine anhydride reaction by a completely different mechanism prompted us to attempt a four-component reaction (4CR). We hypothesized that the thiol could react with an initially formed maleic amide to form amides **7a** and **7b** and thus enable a four-component reaction. We were delighted to find that combining benzyl amine, maleic anhydride (**9**), *p*-thiocresol (**10**), and benzaldehyde in toluene at reflux produced lactam **11** in high yield (Scheme 2). Benzaldehyde dimethyl acetal can be used in place of

Scheme 2. One-Pot, Four-Component Reaction (4CR)



benzaldehyde, but the yield is lower. In each case, >95% selectivity for the 4,5-*syn* isomer was observed.

The 4CR of thiols, amines, and aldehydes with maleic anhydride works well for a variety of substrates (eq 2, Figure 1). Alkyl primary amines can be α- or *β*-branched, as

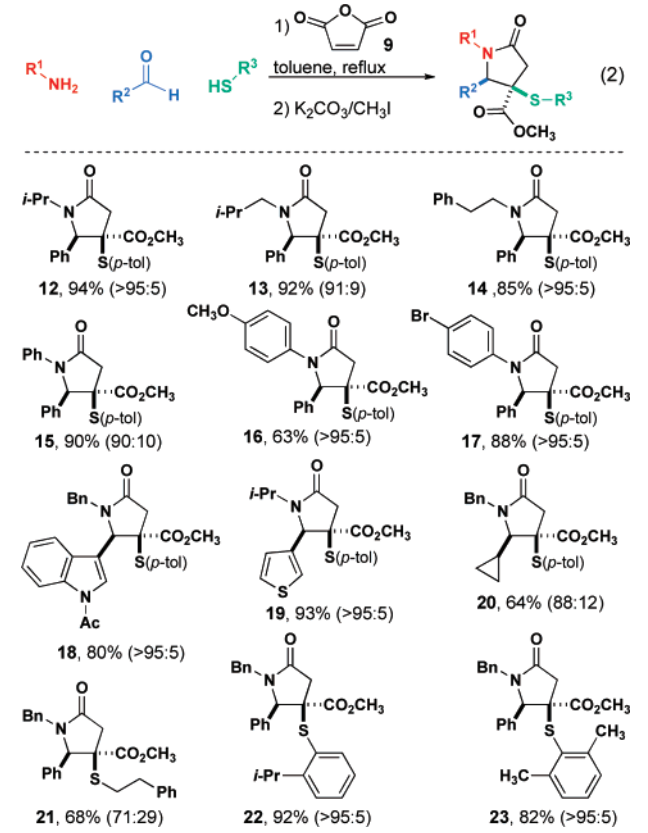


Figure 1. One-pot, four-component syntheses of tetrasubstituted *γ*-lactams (*p*-tol = *p*-$C_6H_4CH_3$). All reactions were conducted by combining the four components in equimolar ratios and heating to reflux in toluene for 24 h. Yields are reported for conversion to the methyl ester and purification by flash chromatography (see Supporting Information).

previously reported for the imine−anhydride reaction, and in this case, anilines now produce *N*-aryl lactams in excellent yields. Although the reaction is limited to nonenolizable aldehydes due to enamide formation, the successful reaction of cyclopropane carboxaldehyde demonstrates that enolization only needs to be energetically suppressed and not completely prevented. The thiol component can be aryl- or alkyl-substituted, though in the latter case the diastereoselectivity is reduced.[13] Ortho-substitution on the thiols is well tolerated, opening the possibility for asymmetric induction from a substituent with a stereogenic center. Given the importance of *γ*-lactams in drug discovery and natural

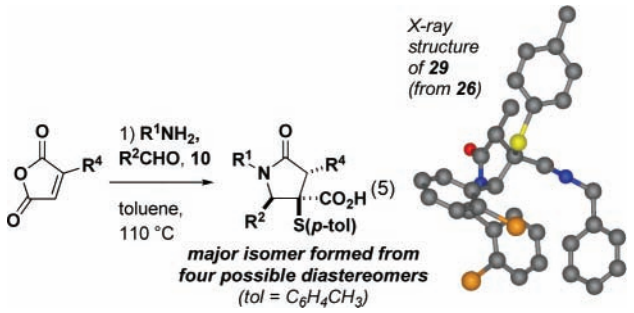
(12) See Supporting Information. A related 3CR with homophthalic anhydride has been observed: Yadav, J. S.; Reddy, B. V. S.; Saritha Raj, K.; Prasad, A. R. *Tetrahedron* **2003**, *59*, 1805−1809.

(13) The *S*-aryl compounds are useful substrates for radical reactions. See: (a) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 1949−1956. (b) Alibes, R.; Bayon, P.; De March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Org. Lett.* **2006**, *8*, 1617−1620. (c) Ghosh, S.; Sinha, S.; Drew, M. G. B. *Org. Lett.* **2006**, *8*, 3781−3784.

product synthesis, we anticipate that the wide substrate tolerance will enable the preparation of useful synthetic intermediates.

Pentasubstituted lactams can be prepared from 3-substituted maleic anhydrides (eq 3, Table 1) with high (>83%)

Table 1. 3-Substituted Maleic Anhydrides



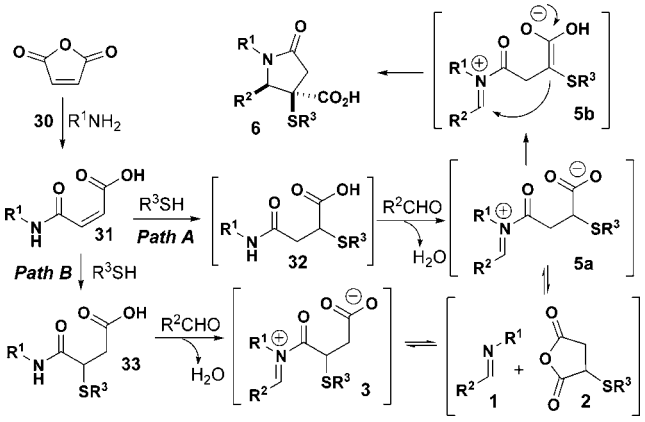
entry (product)	R^1	R^2	R^4	yield[a,b]	ds
1 (**24**)	*i*-Pr	Ph	CH_3	70%	86%[c]
2 (**25**)	Bn	Ph	CH_3	65%	83%[d]
3 (**26**)	*o*-BrC_6H_5	*o*-BrC_6H_5	*i*-Bu	49%[e]	–[f]
4 (**27**)	*i*-Pr	Ph	*i*-Bu	68%	83%[d]
5 (**28**)	Bn	Ph	*i*-Bu	62%	–[f]

[a] Combined yield of product mixture after conversion to the methyl ester (see Supporting Information). [b]Major isomer out of the mixture of up to four isomers. [c]Based on GC analysis of the unpurified mixture of methyl esters. [d]Lower limit based on analysis of ^{1}H NMR spectroscopy. [e]Yield of isolated major diastereomer based on conversion of the intermediate acid to benzyl amide **29** and isolation of the major diastereomer (see Supporting Information). [f]Baseline resolution of a minor isomer was not possible using GC or HPLC.

diastereoselectivity for the formation of one of the four possible diastereomers. Methyl and isobutyl[14] substituents both exhibit high selectivity. The configuration of acid **26** (entry 3) was determined by conversion to benzyl amide **29** and X-ray crystallographic analysis. We are currently investigating the origin of the high diastereoselectivity observed in this reaction.

The mechanism of this new 4CR relies on the ability of both regioisomers of the initially formed maleic amide to converge on a single regioisomer of the iminium ion capable of proceeding to the lactam product (Scheme 3). Reaction of amine **30** with maleic anhydride is rapid at ambient temperature, while the subsequent conjugate addition of the thiol to the amide in the absence of base[15] is slower and proceeds at elevated temperatures. Thiols are known to react

Scheme 3. Mechanism of the One-Pot, 4CR[a]



[a] Iminium ion **3** (path B) equilibrates with iminium ion **5a** (path A) to proceed on to product.

at either terminus (paths A and B, Scheme 3) of the double bond of unsymmetrical maleic amides, depending on the conditions.[16] Condensation with the aldehyde results in the formation of the iminium zwitterions **5a** and **3**, from paths A and B, respectively. In the case of path A, iminium ion **5a** can tautomerize at the thio-substituted carboxylate to form enolate **5b**, which proceeds on to product. In the case of path B, iminium ion intermediate **3** intermediate can partition to imine **1** and anhydride **2**, which can recombine to iminium ion **5a** and proceed on to the observed product. The mechanism for the formation of the pentasubstituted lactam products is complicated by regioselectivity of the reactions of substituted maleic anhydrides,[17] and further control experiments will be required to fully dissect this process.

The products of the 4CR are useful precursors to stereochemically defined trisubstituted lactams. Radical reductive desulfurization yields the corresponding disubstituted carboxy lactam *syn*-**34** in high yield and with high diastereoselection (Scheme 4).[18] The 4,5-*anti* diastereomer of **34** is easily

(14) Alkyl-substituted maleic anhydrides are easily prepared from Grignard reagents and dimethylacetylene dicarboxylate: (a) Scholte, A. A.; Eubanks, L. M.; Poulter, C. D.; Vederas, J. C. *Bioorg. Med. Chem.* **2004**, *12*, 763−770.

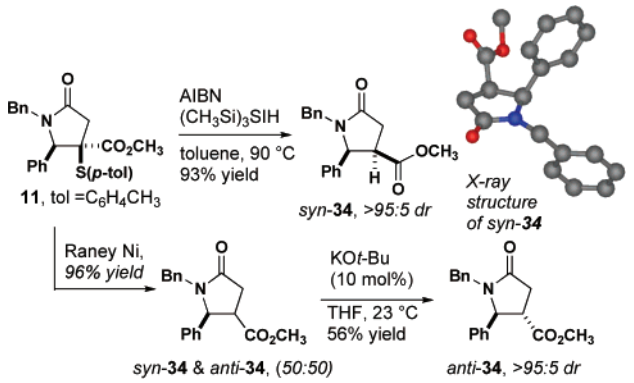
(15) See refs 16a and 16b. The reaction of the thiol with the anhydride in the presence of base is rapid at room temperature: Zienty, F. B.; Vineyard, B. D.; Schleppnik, A. A. *J. Org. Chem.* **1962**, *27*, 3140−3146. When the thiol, amine, and anhydride are combined at rt, some of the thio-substituted anhydride could form since the addition of the amine to the anhydride is probably competitive with the base-mediated conjugate addition of the thiol. Compounds **31**−**33** are all observed in the crude reaction mixture before the reaction mixture is heated to induce the condensation with the aldehyde.

(16) The conjugate addition of thiols to maleic monoamides has been reported to occur at the β-carbon of the amide: (a) Augustin, M.; Mueller, W. *Z. Chem.* **1985**, *25*, 61−62. (b) Neumann, R.; Ringsdorf, H. *J. Am. Chem. Soc.* **1986**, *108*, 487−490. The presence of the other regioisomers is not ruled out in either report. For related studies on thiol conjugate addition to mixed amide/ester and ester/acid maleates, see: (c) Augustin, M.; Koehler, M. *Tetrahedron* **1976**, *32*, 2141−2145. (d) Tomioka, K.; Muraoka, A.; Kanai, M. *J. Org. Chem.* **1995**, *60*, 6188−6190. (e) Kamimura, A.; Murakami, N.; Kawahara, F.; Yokota, K.; Omata, Y.; Matsuura, K.; Oishi, Y.; Morita, R.; Mitsudera, H.; Suzukawa, H.; Kakehi, A.; Shirai, M.; Okamoto, H. *Tetrahedron* **2003**, *59*, 9537−9546. (f) Kamimura, A.; Murakami, N.; Yokota, K.; Shirai, M.; Okamoto, H. *Tetrahedron Lett.* **2002**, *43*, 7521−7523. (g) Schmidt, T. J.; Ak, M.; Mrowietz, U. *Bioorg. Med. Chem.* **2007**, *15*, 333−342.

(17) (a) Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012−1015. (b) Baydar, A. E.; Boyd, G. V.; Aupers, J.; Lindley, P. F. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 2890−2894. Mehta et al. report that primary amines react unselectively with 3-methylmaleic (citraconic) anhydride, whereas secondary amines were reported to react with >95% regioselectivity. The subsequent report from Baydar demonstrates that these findings were incorrect and that both primary and secondary amines exhibit 50:50 to 78:22 regioselectivity.

(18) (a) Natsugari, H.; Matsushita, Y.; Tamura, N.; Yoshioka, K.; Ochiai, M. *J. Chem. Soc., Perkin Trans.* **1983**, *1*, 403−411. (b) Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010−3017.

Scheme 4. Stereoselective Synthesis of 4,5-*syn*- and 4,5-*anti*-γ-Lactams



accessed by desulfurization with Raney nickel to a mixture of diastereomers that can be epimerized with potassium *tert*-butoxide at ambient temperature to yield a single isomer of product.

We have demonstrated that densely substituted γ-lactams are formed from a remarkable four-component reaction that forms up to three stereogenic centers in a single step. This reaction should prove useful in the rapid synthesis of collections of compounds for the discovery of drugs and biological probes. We are currently pursuing the synthesis of several natural product targets using this transformation.

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Supporting Information Available: Experimental procedures for the preparation of all new compounds and X-ray crystallographic data for **29** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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