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Preparation of γ- and δ-Lactams by Ring Closure of β,γ-Unsaturated Amides using Trifluoromethanesulfonic Acid

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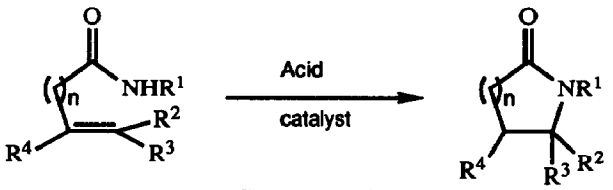
Abstract: γ-Lactams and δ-lactams can be prepared by the reaction of β,γ-unsaturated amides with trifluoromethanesulfonic acid.

Substituted lactams constitute a central and important area of synthetic organic, medicinal and pharmacological chemistry.[1] Of the numerous routes to medium ring lactams,[2] cyclodehydration of ω-amino acids is one of the simplest.[2a] The Beckmann rearrangement[2b,2c,2d] and Schmidt reaction[2e] are other common routes, but any such ring expansion[2] by insertion of a nitrogen atom adjacent to a carbonyl group that requires the ketone as starting material is unsuitable for the synthesis of γ-lactams unless the cyclobutanone is readily available, which is not usually the case.

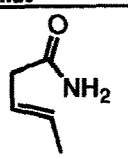
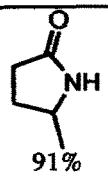
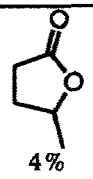
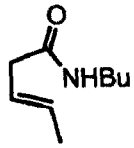
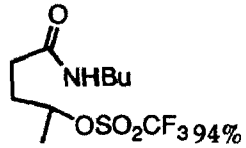
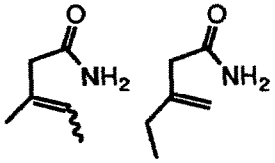
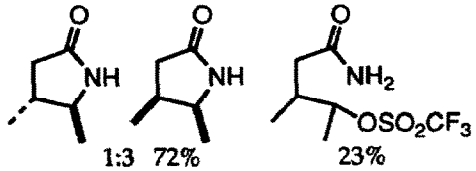
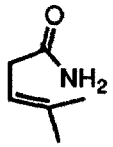
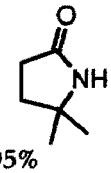
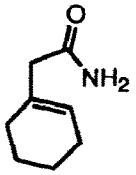
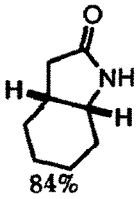
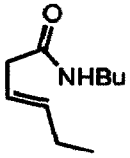
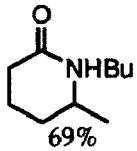
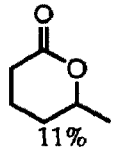
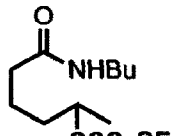
In seeking a general, and direct route to lactams from acyclic precursors, an analogy with the long-known acid-catalyzed cyclizations of unsaturated carboxylic acids to lactones[3] presented itself (Scheme 1). The problem of cyclization onto an unactivated double bond therefore arose. Cyclization of amidic nitrogen onto unactivated C=C bonds[4a] has been



Scheme 1

achieved with a variety of reagents including $Hg(OAc)_2$,[4b,4c] PhSeCl,[4d] and TMSOTf-I_2.[4e] Addition of amides to activated C=C bonds, including α,β-unsaturated nitriles[5,6] and vinyl sulfones[6] is known. However, the acid-catalyzed amidation of an unactivated C=C bond is rare, and chiefly or exclusively confined to the formation of a quaternary carbon centre *alpha* to the nitrogen atom of the resulting lactam.[7]

Cyclization of β,γ-Unsaturated Amides using Trifluoromethanesulfonic Acid

	β,γ-Unsaturated amide	Reaction time (hours)	Products
1.		0.75	 91%  4%
2.		48	 94%
3.	 1:1	16	 1:3 72% 23%
4.		2	 95%
5.		4	 84%
6.		16	 69%  11%  14%

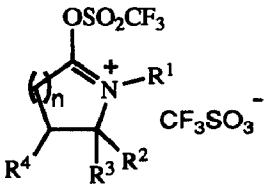
We now report that a variety of substituted γ- and δ-lactams can be prepared by reaction of β,γ-unsaturated amides[8] with trifluoromethanesulfonic acid.[9] The Table shows the products[10] obtained by reaction of various β,γ-unsaturated amides with CF_3SO_3H in CH_2Cl_2. Taking entry 1 as a representative example, *(E)*-3-pentenamide (0.99g, 10.0 mmol) was dissolved in a mixture of CF_3SO_3H (5.0 ml) and dichloromethane (20 ml) and stirred at 20°C

under an atmosphere of nitrogen. The reaction period was determined by monitoring the disappearance of the α,β–unsaturated amide by thin-layer chromatography. Upon completion, the mixture was cooled in ice, treated with saturated aqueous sodium hydrogen carbonate (dropwise at first), and extracted with dichloromethane (3X30 ml). The combined extracts were dried (Na_2SO_4), the solvent removed and the residue chromatographed (silica, EtOAc:EtOH, 95:5) to give first 5-methyl-γ-butyrolactone and subsequently 5-methylpyrrolidin-2-one. In all cases, the lactam was readily separated by column chromatography from either the minor quantity of lactone or amidic trifluoromethanesulfonate, in cases where these were formed.

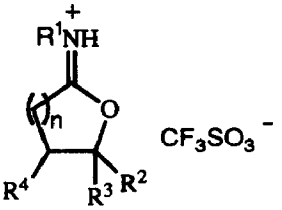
A notable feature of the cyclizations giving γ- or δ-lactams (Table) is the efficient formation of a new tertiary carbon centre (entries 1, 3, 5 and 6). Entry 5 shows that cyclization is effective with an alicyclic ring fused at the γ and δ-positions; the stereocontrol was high, and the configuration was confirmed as the *cis*-fused lactam[11] by an n.O.e. enhancement of the signal (5%) for the 3a-hydrogen atom signal at δ 2.04 upon irradiation of the signal assigned as the 7a-hydrogen atom (δ 3.64). Similarly, the *cis*-disubstituted lactam predominates in entry 3; although the *cis*- and *trans*-lactams could not be separated by chromatography, all ^1H and ^{13}C NMR signals were assignable. Irradiation of the H-5 hydrogen atom signal (δ 3.75) in the ^1H NMR spectrum of the *cis*-lactam (entry 3) gave an n.O.e. enhancement (4%) of the H-4 hydrogen atom signal at δ 2.16.[11]

The formation of trifluoromethanesulfonates in some cases (entries 2 and 3) evidently indicates competition for attack at the cationic centre: intermolecularly by attack of trifluoromethanesulfonate anion *versus* internally by one or other of the amide termini. The difference in behaviour of two *N*-butylamides (entries 2 and 6) both as compared to each other, and also in contrast with entries 1, 3, 4 and 5, suggests that either the relative nucleophilicity of the amide or the size of ring being formed, and probably both factors, are relevant to the fine balance that determines the constitution of the cyclized products. The exclusive formation of α-methyl trifluoromethanesulfonates, regardless of the initial location of the alkenic bond (entries 3 and 6) is consistent with acid-catalyzed migration of the double bond such that some terminally alkenic amide is formed; protonation and nucleophilic attack would then account for the products, although this has yet to be demonstrated.

The formation of the lactams may proceed through alkyl iminotrifluoromethanesulfonates or their salts **1**. The intermediacy of alkyl iminosulfates[12] in the Ritter reaction[13] has been established. The formation of trifluoromethanesulfonates (entries 2 and 3) may be a consequence of slow ring-closure to the corresponding lactams (or lactones) owing to developing 1,2-eclipsing interactions. The formation of the lactones most probably proceeds through salts of cyclic imino-ethers[14] such as **2**. The scope and synthetic applications of these cyclizations are being investigated.



1 R^1=H, alkyl



2 R^1=H, alkyl

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References and Notes:

1. Huisman, H. O. in 'MTP International Review of Science, Organic Chemistry Series One', ed. Hey, D. H., Butterworth, London, 1973, vol. 8, 235; Challis, B. C.; Challis, J. A. in 'Comprehensive Organic Chemistry', eds. Barton, D. H. R. and Ollis, W. D., Pergamon Press, Oxford, **1979**, vol. 2, pp. 976-980; Lowe, G. 'β-Lactam Antibiotics', in Comprehensive Organic Chemistry', eds. Barton, D. H. R. and Ollis, W. D., Pergamon Press, Oxford, **1979**, vol. 5, pp. 289-320.
2. (a) Blade-Font, A. *Tetrahedron Lett.*, **1980**, 2443 (b) Gawley, R. E. *Org. React.* (N.Y.), **1987**, *35*, 1 (c) Krow, G. R. *Tetrahedron*, **1981**,1283 (d) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.*, **1989**, *30*, 4207 (e) Koldobski, G. I.; Tereshchenko, G. F.; Gerasimova, E. S.; Bagal, L. I. *Russ. Chem. Rev.*, **1971**, *40*, 835.
3. M. F. Ansell and M. H. Palmer, *Quart. Rev. Chem. Soc.*, **1964**, 211.
4. (a) Staninets, V. I.; Gevaza, Yu. I. *Khim. Geterotsikl Soedin.*, **1985**, 435 (b) Wilson, S. R.; Sawicki, R. A. *J. Heterocycl. Chem.*, **1982**, *19*, 81 (c) Larock, R. C. in 'Solvomercuration/Demercuration Reactions in Organic Synthesis', Springer Verlag, Berlin, **1986**, Chap. 7 (d) Toshimitsu, A.; Terao, K.; Vemura, S. *Tetrahedron Lett.*, **1984**, *25*, 5917 (e) Knapp, S.; Rodriques, K. E.; Levorse, A. T.; Ornaf, R. M. *Tetrahedron Lett.*, **1985**, *26*, 1803.
5. Mariella, R. P.; Jonauskas, R. *J. Org. Chem.*, **1958**, *23*, 923.
6. Batty, J. W.; Howes, P. D.; Stirling, C. J. M., *J. Chem. Soc., Perkin Trans 1*, **1976**, 1543.
7. (a) Hill, R. K. , *J. Org. Chem.*, **1957**, *22*, 830 (b) Wittekind, R. R.; Weissman, C.; Farber, S.; Meltzer, R. I. *J. Heterocycl. Chem.*, **1967**, *4*, 143 (c) Tilley, J. W.; Clader, J. W.; Wirkus, M.; Blount, J. F. *J. Org. Chem.*, **1985**, *50*, 2220.
8. Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.*, **1991**, *56*, 2603; Marson, C. M. ; Grabowska, U.; Walsgrove, T. *J. Org. Chem.*, **1992**, *57*, 5045.
9. Stang, P. J.; White, M. R. *Aldrichimica Acta.*, **1983**, *16*, 15.
10. New compounds gave satisfactory elemental analyses or high resolution mass spectral data, and exhibited spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) in agreement with their structures.
11. For related cyclizations giving *cis*-ring junction stereochemistry, see: Takahata, H.; Takamatsu, T.; Mozumi, M.; Chen, Y.-S.; Yamazaki, T.; Aoe, K. *J. Chem. Soc., Chem. Commun.*, **1987**, 1627. An analogous bromolactonization afforded a β-lactone in addition to the *cis*-fused lactone: Cambie, R. C.; Rutledge, P. S.; Somerville, R. F.; Woodgate, P. D. *Synthesis*, **1988**, 1009.
12. Glikmans, G.; Torck, B.; Hellin, M.; Coussemant, F.; *Bull. Soc. Chim. Fr.*, **1966**, 1376;
13. Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.*, **1948**, *70*, 4045; Krimen, L. I.; Cota, D. J. *Org. React (N. Y.)*, **1969**, *17*, 213.
14. Stirling, C. J. M. *J. Chem. Soc.*, **1960**, 255.

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