High-Pressure-Promoted (2 + 2) Cycloadditions of Imines with Electron-Rich Alkenes. A Simple Route to Azetidines and β-Amino Carbonyl Compounds

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The synthetic scope of high-pressure-promoted (2 + 2) cycloadditions between imines and electron-rich alkenes has been investigated. For the first time it has been possible to isolate an azetidine from the reaction of the strong electron-rich 1-pyrrolidino-2-methylpropene and *N*-methyl- or *N*-phenylimines of benzaldehyde. The azetidines obtained decompose slowly at normal pressure, even at room temperature. Enamines with β-hydrogen do not yield azetidines but open products in the reaction with imines. Hydrolysis of the azetidines as well as the open products yield β-amino carbonyl compounds. The high-pressure reaction combined with the hydrolysis has been used as a one-pot process for the synthesis of a variety of β-amino carbonyl compounds. The scope of the (2 + 2) cycloadditions of the moderate electron-rich ketene acetals and the weak electron-rich enol ethers with several imines could be largely extended by using high pressure. The *N*-toluenesulfonylimine of benzaldehyde reacted with a variety of enol ethers having an α-hydrogen to give azetidines. A moderate to high stereoselectivity was found in these cycloadditions. The azetidines could easily be hydrolyzed to β-amino aldehydes. The stereochemistry of these reactions has been discussed.

Polar (2 + 2) cycloadditions of electron-rich alkenes with electron-poor double bonds (e.g., C=C and C=O bonds) have appeared to be simple and stereoselective routes to four-membered ring compounds. The cycloadducts derived from alkoxy- or amino-substituted alkenes can generally be further hydrolyzed into open carbonyl compounds in which the stereochemistry is maintained.[1]

Although the most straightforward route to azetidines (and concomitant β-amino carbonyl compounds) should be a polar (2 + 2) cycloaddition between an imine and an electron-rich alkene, this reaction has been restricted in the literature to a few exceptional examples. Weak electron-rich enol ethers react only with imines which are strongly activated by three electron-withdrawing substituents.[2] Nonactivated imines have been reported to react in polar solvents with strong electron-rich enamines. Azetidines, however, have only sometimes been claimed as reaction intermediates.

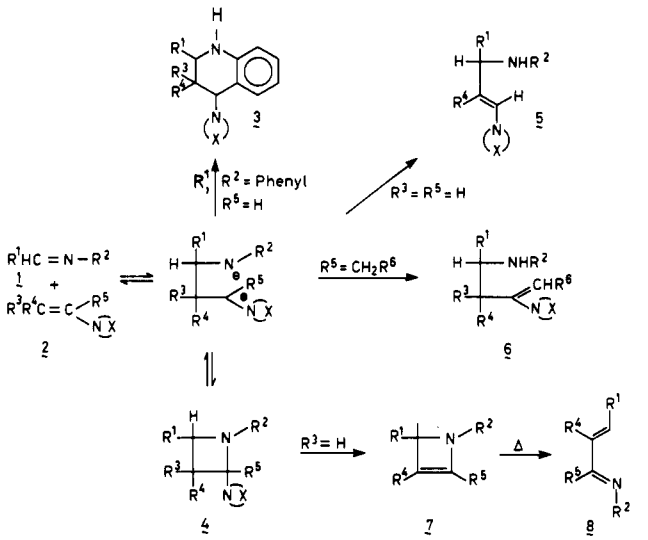
In previous papers we have shown that the scope of polar (2 + 2) cycloadditions can be broadly extended by applying high pressure.[3,4] The formation of one bond together with the formation of a dipolar charge in the transition state causes a strong decrease of the reaction volume. Therefore polar (2 + 2) cycloadditions have large negative activation volumes which are in the same order of magnitude as those found for Diels–Alder reactions.[5,6]

Now we have investigated whether the scope of the polar (2 + 2) cycloadditions between imines and electron-rich alkenes can be extended by applying high pressure and how pressure can effect the stereochemistry of these cycloadditions.

Reactions of Imines with Enamines

There are several reports in the literature about the reactions of the strong electron-rich enamines derived from cyclic secondary amines (e.g., pyrrolidine, piperidine, morpholine) with imines.

Scheme I



A variety of products have been obtained depending on reaction circumstances and substitution pattern of the enamines and imines. Azetidines have sometimes been claimed as reaction intermediates, but they have not been isolated. The main reaction routes have been pictured in Scheme I.

The reactions of cyclic enamines with benzylidene anilines ($R^1 = R^2$ = phenyl) were first studied by Tomoda et al.[7] Products of type **6** were isolated in the very polar solvent methanol. When performed in acetic acid this reaction has led to tetrahydroquinoline derivatives **3**, which are supposed to be formed via (4 + 2) cycloaddition.[8]

An initial (2 + 2) cycloaddition between an enamine and an imine with $R^1 = R^2$ = aryl has been supposed to explain the formation of the 1-aza-1,3-diene **8** in acetic acid as the solvent.[9] The scope of this synthesis of **8** has been further

(1) Scheeren, J. W. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 71.
(2) Moore, J. A.; Ayers, R. S. In *Heterocyclic Compounds*; Hassner, A., Ed.; Wiley: New York, 1983; Vol. 42, part 2, p 123 and references cited therein.
(3) Aben, R. W. M.; Scheeren, J. W. *Tetrahedron Lett.* **1983**, *24*, 4613.
(4) Aben, R. W. M.; Scheeren, J. W. *Tetrahedron Lett.* **1985**, *26*, 1889.
(5) Sasaki, M.; Tsuzuki, H.; Osugi, J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1596.
(6) van Jouanne, J.; Kelm, H.; Huisgen, R. *J. Am. Chem. Soc.* **1979**, *101*, 151.
(7) Tomoda, S.; Takeuchi, Y.; Nomura, Y. *Tetrahedron Lett.* **1969**, 3549.
(8) Nomura, Y.; Kimura, M.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1978**, 267.
(9) Nomura, Y.; Kimura, M.; Shibata, T.; Takeuchi, Y.; Tomoda, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3343.

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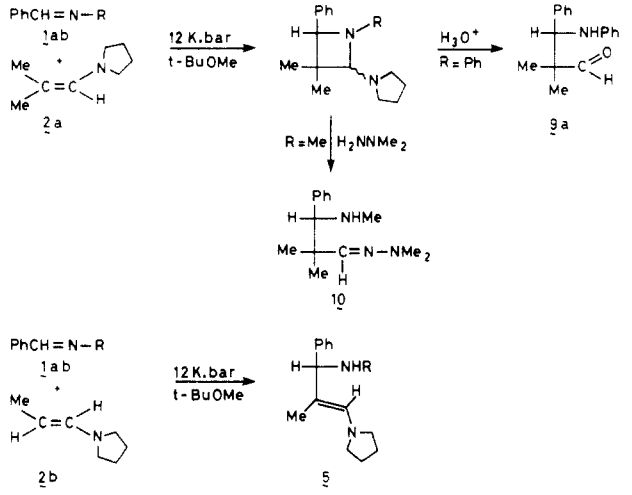
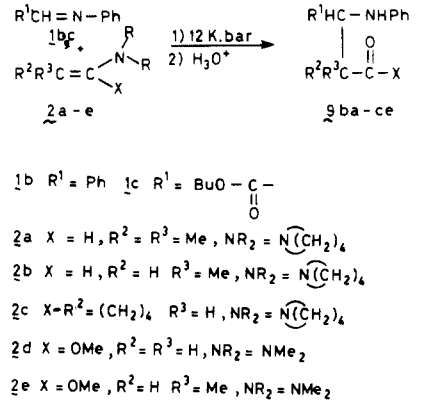
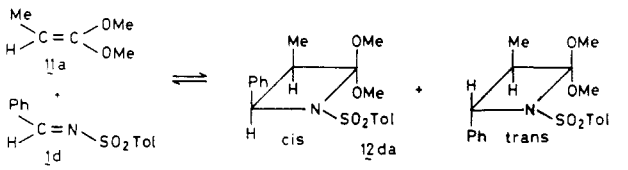
Scheme II



Scheme III



Scheme IV



Benzene 5 min	80%	20%
Benzene 18 hrs	40%	60%
Acetonitrile 5 min	40%	60%

studied with other imines by Komatsu et al.[10]

The results of the above suggest that azetidines may be isolated from the reaction of imines with enamines when the cycloaddition is performed in a weak polar solvent so that the dipolar intermediate is not stabilized and is not intercepted by the solvent. Furthermore, the elimination of a proton leading to product **5** or **6** should be avoided. The enamines **2** meeting this criteria ($R^3 = R^4$ = alkyl, R^5 = H) are, however, not reactive enough to react at normal pressure. Furthermore, the cycloaddition is strongly depressed in nonpolar solvents. Orientating experiments at normal pressure showed that the nonactivated imines **1a** (R^1 = phenyl, R^2 = Me) and **1b** ($R^1 = R^2$ = phenyl) did not react with enamine **2a** ($R^3 = R^4$ = Me, R^5 = H) in *tert*-butyl methyl ether at room temperature. The same was found when the more activated imine **1c** (R^1 = BuOC(O)) was used. Higher reaction temperatures seemed to us inappropriate in view of the expected instability of the azetidines.

At a pressure of 12 kbar the imine **1a** could be converted with **2a** in 100% excess completely into an azetidine (**4**) in the nonpolar solvent *tert*-butyl methyl ether (see Scheme II). After careful removal of excess **2a** and the solvent at room temperature and at low pressure, the azetidine remained in a purity of about 90%. The proton NMR spectrum shows two CH_3 proton peaks at a distance of 0.4 ppm of each other.

Such large shift differences for geminal methyl groups with a neighboring aryl group have also been found in the corresponding oxetanes.[11] The formed azetidine appeared to be unstable at normal pressure. Even at room temperature it slowly decomposes into starting compounds. Analogous results have been found for the reaction of **1b** with **2a**. The unstable azetidines could, however, be easily further transformed into stable products by hydrolysis or by reaction with dimethylhydrazine (see Scheme II).

The reactions of **1a** and **1b** with the enamine **2b**, having a β-hydrogen, yielded under the same reaction circumstances a more complex reaction mixture. The presence of a vinylic proton at 5.4 ppm in the proton NMR spectrum of the reaction mixture, after careful removal of volatile products, points to the formation of the open product **5**. Enamine **2e** appeared considerably less reactive than **2d**. No conversion was observed at room temperature between **1b** and **2e** after 20 h at 12 kbar. The more reactive imine **1c** also yielded with enamines under high pressure in nonpolar solvents complex reaction mixtures which were difficult to purify.

The experiments described above show that azetidines derived from enamines are unstable at normal pressure. Furthermore it appears that formation of open products cannot be avoided by working at high pressure. We envisaged, however, that azetidines **4** as well as the open products **5** and **6** can be hydrolyzed into the same β-amino carbonyl compounds (**9**). Therefore, for synthetic purposes the reaction mixtures obtained under high pressure were directly hydrolyzed into β-amino carbonyl compounds as given in Scheme III.

By this reaction sequence a variety of β-amino carbonyl compounds (**9**) were synthesized via a one-pot procedure. In cases where two diastereomers can be formed, e.g., the reaction of **1c** with **2c** and **2e**, one isomer is favored.

For compound **9cc** the erythro isomer, which is 70% of the diastereomeric mixture, could be isolated by preparative HPLC followed by crystallization from diisopropyl ether. The structure was determined by X-ray analysis.

Compound **9ce**, which is 80% of the diastereomeric mixture, was purified by HPLC. The coupling constant J_{HaHb} = 5 Hz between the α- and β-hydrogen points also to a erythro isomer.[12]

(10) Komatsu, M.; Takamatsu, S.; Uesaka, M.; Yamamoto, S.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1984**, *49*, 2691.

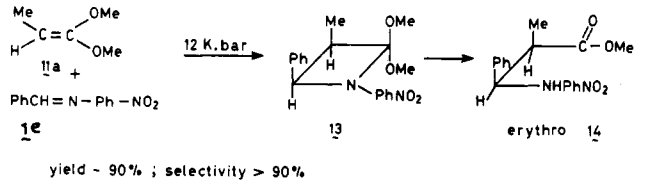
(11) (a) Scheeren, H. W.; Aben, R. W. M.; Ooms, P. H. J.; Nivard, R. J. F. *J. Org. Chem.* **1977**, *42*, 3128. (b) Hofstraat, R. G.; Scheeren, J. W.; Nivard, R. J. F. *J. Chem. Soc., Perkin Trans. 1* **1985**, 561.

(12) Note: In an analogous way as for β-hydroxy esters the configuration threo or erythro of β-amino carbonyl compounds can be deduced from the H(2)–H(3) coupling constants. The threo is supposed to have the larger coupling constant than the erythro isomer. We realize, however, that these suppositions have to be taken with great care as it has been demonstrated that these coupling constants of both threo and erythro compounds depend strongly on the size of the substituents at the α and β carbon atom.[13b,14] For β-amino esters having a primary alkyl substituent at the α carbon atom and phenyl groups at the β carbon and nitrogen atom H(2)–H(3) coupling constants of 5.7–5.8 Hz have been reported.[14]

(13) (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. I. *J. Am. Chem. Soc.* **1973**, *95*, 3310. (b) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(14) Dardoize, F.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1976**, 1561.

Scheme V



yield ~ 90% ; selectivity > 90%

Reactions of Imines with Ketene Acetals and Enol Ethers

The moderate electron-rich ketene acetals $R^1R^2C{=}C(OMe)_2$ (11) appeared to react at normal pressure with the imine **1d** having the strong electron-withdrawing tosyl group at the nitrogen atom. From the ketene acetal **11a** and the imine **1d** a mixture of *cis*- and *trans*-azetidines was formed, the ratio of which is dependent on the reaction circumstances (see Scheme IV). The results given in the scheme have been determined by proton NMR measurements.

The cis benzylic proton is at lower field and has a larger coupling constant (J = 9 Hz) than the trans benzylic proton (J = 5 Hz). Furthermore, the methyl group which is in cis position of the phenyl group is at higher field than the methyl group which is in the trans position of the phenyl group. The same differences in proton NMR spectra have been described for the corresponding *cis*- and *trans*-oxetanes.[11,15]

From these results it appeared that under kinetic circumstances (short reaction times, nonpolar solvent) the *cis*-azetidine is the main product, whereas under thermodynamic circumstances (prolonged reaction times and/or polar solvent) the *trans*-azetidine is favored. As the cycloaddition at room temperature comes to an equilibrium, the azetidines could not be isolated as pure compounds. A stable azetidine could, however, be obtained from the ketene acetal **11b** ($(MeO)_2C{=}C(OMe)_2$). This is in accordance with the generally observed stability of products obtained from this ketene acetal.[15] At normal pressure the weakly activated imine **1e** did not react with ketene acetals.

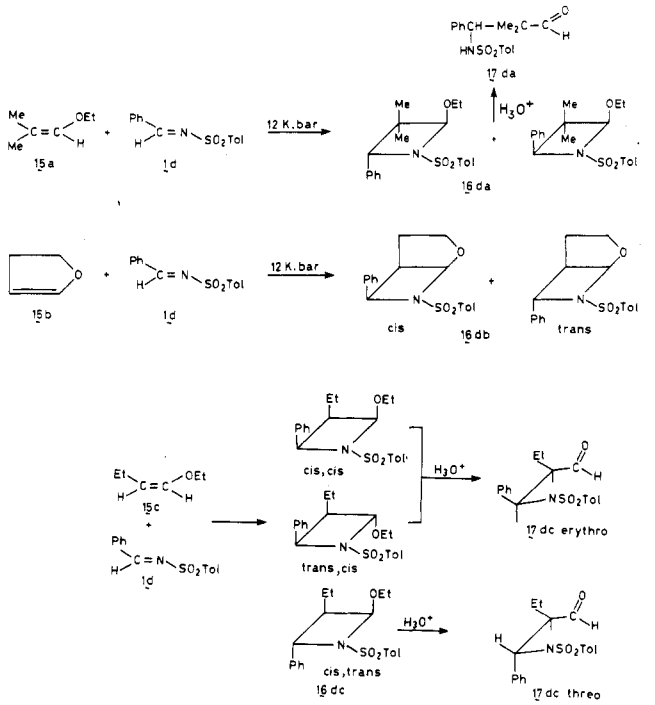
After 12 h at 12 kbar, complete conversion was, however, observed for the cycloaddition between ketene acetal **11a** and the imine **1e** as given in Scheme V.

It appeared from the NMR spectrum of the reaction mixture that the *cis*-azetidine was now formed with a selectivity of at least 90%. Clearly the cycloaddition is not in equilibrium so that the more favorable kinetic product is selectively formed. The β-amino ester which was obtained after hydrolysis of the main cycloadduct has a coupling constant between α- and β-protons of 5 Hz which points to the expected erythro ester.[12]

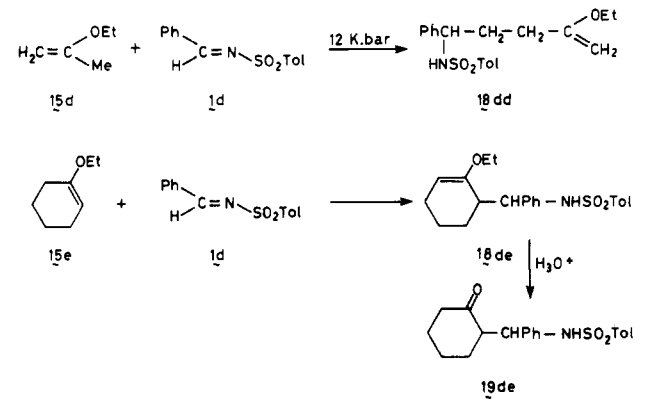
No reaction even after prolonged heating has been observed between enol ethers and the imine **1d** at normal pressure. Enol ethers having a hydrogen in the α-position could be easily converted, however, into azetidines under a pressure of 12 kbar at a temperature of 50 °C. The stereochemical results for three representative enol ethers have been presented in Scheme VI. The ratio 9:1 for the azetidine obtained from **15a** and **1d** could easily be determined by integration of the protons at the carbons bearing the phenyl and the ethoxy group which have different shifts for the two isomers. Hydrolysis of the reaction mixture yielded as expected only one β-amino aldehyde (**17da**).

From the cycloaddition of dihydrofuran **15b** and **1d** two azetidines had been obtained in a ratio 8:1 (from NMR).

Scheme VI



Scheme VII



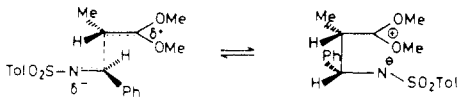
We suppose that the main product, having the larger coupling constant for the doublet of the H–C–Ph proton, has the cis configuration. The main product could easily be obtained pure by crystallization from diisopropyl ether.

Reaction of the *cis*-1-ethoxy-1-butene (**15c**) with **1d** gave in a good yield of 80% a mixture of three azetidines. The main product crystallized partly from the reaction mixture after addition of diisopropyl ether. The remaining oil could be separated in three azetidines by HPLC in the ratio 5:2:6. The two azetidines with the larger coupling constants for the doublet of the H–C–Ph protons (J = 9 Hz) were supposed to be azetidines with the phenyl and ethyl group in cis position but with different positions for the ethoxy group. Indeed, both azetidines could be hydrolyzed into the same β-amino aldehyde. The formation of both cis isomers shows that under the high pressure circumstances (12 kbar, 50 °C) the original cis configuration present in the enole ether has partly lost. This probably occurs by rotation around the corresponding C–C bond in the dipolar intermediate. These phenomena have also been observed in (2 + 2) cycloadditions of enol ethers and TCNE at normal pressure.[16] The fourth possible isomer was

(15) Scheeren, H. W.; van Rossum, A. J. R.; Nivard, R. J. F. *Tetrahedron* **1983**, *39*, 1345.

(16) (a) Huisgen, R. *Pure Appl. Chem.* **1980**, *52*, 2283. (b) Huisgen, R. *Acc. Chem. Res.* **1977**, *10*, 117 and 199.

Scheme VIII



probably formed in such small amounts that it could not be detected.

No azetidines but only open products of type **6** were isolated from **1d** and the enol ether **15d** having a methyl substituent in the α-position. Probably an intramolecular proton abstraction within the dipolar intermediate is also faster under high pressure than ring closure to azetidines (Scheme VII).

Discussion

In all the (2 + 2) cycloadditions performed under high pressure leading to a stable azetidine the cis product seems to be favored. Before it has been shown that acid-catalyzed (2 + 2) cycloadditions of the ketene acetal MeHC=C-$(OMe)_2$ with aldehydes RCHO[17] yield cis oxetanes as major products when R is not too large.[11b]

The preferred formation of the cis oxetane has been explained via the most favored transoid approach of the cycloaddends when the carbonyl oxygen is complexed with the Lewis acid.

In the absence of Lewis acid and under high pressure the *trans*-oxetane is always the main product. Probably, the transition state is now closer to a cisoid dipolar[3] intermediate because the noncomplexed oxygen has a much smaller size. We suppose that in the cycloadditions of imines having a much more bulky dipolar end, due to the substituents on the nitrogen atom, the more favored transoid approach of the cycloadducts determines the stereoselectivity of the reaction (see Scheme VIII).

Experimental Section

The high-pressure experiments were run in a high-pressure apparatus equipped with a one-wall-piston cylinder for pressures up to 14 kbar (1.4 GPa) having an initial volume of 70 mL. The reaction volume after compression is about 30 mL. The vessel is closed from below with a steel stopper and from above with a mobile piston. Heating occurs by pumping oil between the vessel and a second wall.

Reactions were performed in 8-mL Teflon ampules closed by screwed stainless steel stoppers. Two of these ampules can be inserted into the high-pressure vessel filled with hexane and transmission medium. For analytical purposes or orientating experiments ampules of 0.5 mL can be used so that the conversion in five different experiments can be followed at the same time.

^{1}H NMR spectra were measured on a Hitachi Perkin-Elmer R-24B (60 MHz) spectrometer or when indicated on a Bruker WH-90 spectrometer with Me_4Si as an internal standard. $CDCl_3$ was used as the solvent unless stated otherwise. IR spectra were measured with a Perkin-Elmer Model 997 spectrophotometer. Mass spectra were obtained with a double-focusing VG M-M 7070 E mass spectrometer. Melting points were taken on a Kofler hot stage (Leitz-Wetzlar) and are uncorrected. For column chromatography Merck silica gel H (type 60) was used. The Miniprep LC (Jobin Yvon) was used for preparative HPLC.

Azetidines 4aa and 4ba from the Imines 1a or 1b and the Enamine 2a. An 8-mL Teflon ampule was charged with 5 mmol of the imines **1a** or **1b** and 1.5 g (22 mmol) of the enamine **2a** dissolved in *tert*-butyl methyl ether. Two of these ampules were kept at a pressure of 12 kbar for 24 h. After release of pressure, workup occurred by removal of the solvent and excess of **2a** at low pressure so that the temperature could be kept below 30 °C. In this way azetidine **4aa** was obtained in a purity of about 90%. Further purification was not possible because at normal pressure the azetidine slowly decomposed at room temperature into starting compounds. Azetidine **4aa**: MS, m/e 245 (M + 1), 244, 216, 174, 162, 126; M^+ + 1 calcd 245.2018, found 245.2023; ^{1}H NMR δ 7.17 (br s, 5 H, phenyl), 3.33 (br s, 1 H, $HC(N)_2$), 2.96 (s, 1 H, HCPh), 2.85–2.30 (m, 4 H, NCH_2), 2.33 (s, 3 H, NCH_3), 1.83–1.43 (m, 4 H, CH_2CH_2), 1.13 (s, 3 H, CH_3), 0.73 (s, 3 H, CH_3).

Conversion of the Azetidine 4aa into the Dimethylhydrazone 10. The reaction mixture of **4aa** obtained after release of pressure was mixed with 3 equiv of 1,1-dimethylhydrazine. After standing for 20 min at room temperature, the mixture was concentrated in vacuo, and the remaining oil was purified by bulb-to-bulb distillation: bp 102 °C/0.8 mm, yield 62%; MS, m/e 234 (M + 1), 189, 162; M^+ + 1 calcd 234.1970, found 234.1963. Anal. Calcd for $C_{14}H_{23}N_3$: C, 72.06; H, 9.93; N, 18.01. Found: C, 71.90; H, 9.89; N, 17.65.

One-Pot Preparation for the β-Amino Carbonyl Compounds 9ba, 9ca, 9cc, and 9ce. Two 8-mL Teflon ampules filled with a solution of 0.9 g (5 mmol) of the imine **1b** and 0.75 g (11 mmol) of the imine **2a** in *tert*-butyl methyl ether were kept under a pressure of 12 kbar for 20 h at room temperature. In the same way a solution of 1 g (5 mmol) of **1c** and 6 mmol of the enamines **2a**, **2c**, **2d**, or **2e** were kept under a pressure of 12 kbar for 15 h.

After release of pressure, the reaction mixture was poured into a solution of 1 mL of H_2O and 0.2 g of acetic acid in 10 mL of acetonitrile. The solution was kept for 30 min at room temperature and then diluted with 50 mL of dichloromethane. The organic layer was several times washed with H_2O and then dried over Na_2SO_4. Evaporation of the solvent yielded the crude β-amino compounds which were further purified by bulb-to-bulb distillation and/or crystallization. Yields, boiling points, and some spectroscopic data are collected in Table I. The β-amino aldehyde **9ca** was obtained as an oil which could not be purified by bulb-to-bulb distillation. Therefore it was converted into a phenylhydrazone: mp 97–98 °C; MS, m/e 368 (M + 1), 275, 234, 206. Anal. Calcd for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 71.64; H, 8.15; N, 11.08.

Azetidine 12db from 1d and Tetramethoxyethene 11b. A solution of 1.30 g (5 mmol) of **1d** and 1.52 g (10 mmol) of **11b** in 10 mL of acetonitrile was kept at 80 °C for 24 h. After that the solvent was evaporated in vacuo, and the solid residue was crystallized from methanol: yield 85%; mp 162 °C; MS, m/e 408 (M + 1), 376, 288, 252, 221, 206; ^{1}H NMR δ 7.63 and 7.50 (B part of AB, 2 H, arom), 7.17 (s, 5 H, phenyl), 7.10 and 6.97 (B part of AB, 2 H, arom), 4.57 (s, 1 H, HCPh), 3.63 (s, 3 H, OCH_3), 3.40 (s, 3 H, OCH_3), 3.10 (s, 3 H, OCH_3), 3.03 (s, 3 H, OCH_3), 2.33 (s, 3 H, CH_3). Anal. Calcd for $C_{20}H_{25}NSO_6$: C, 58.95; H, 6.18; N, 3.44. Found: C, 58.71; H, 6.11; N, 3.32.

Azetidine 13 from the Imine 1e and 1,1-Dimethoxypropene (11a). A solution of 0.45 g (2 mmol) of **1e** and 0.35 g (3 mmol) of **11a** in 8 mL of acetonitrile was kept under a pressure of 12 kbar for 20 h at room temperature. After release of pressure the solvent was evaporated in vacuo. The remaining oil was extracted with pentane in order to remove excess of **11a**. Evaporation of the pentane left **13** in a purity of about 90%; yield 90%. To avoid decomposition **13** was not further purified: MS, m/e 329 (M + 1), 297, 255, 227, 211, 196, 103; $(M^+ + 1)/e$ calcd 329.1501, found 329.1502; ^{1}H NMR δ 8.05 and 7.90 (B part of AB, 2 H, arom), 7.30 (br s, 5 H, phenyl), 6.62 and 6.78 (A part of AB, 1 H), 4.93 (1 H, d, J = 9 Hz HCPh), 3.60–3.15 (m, H, partly hidden under CH_3O), 3.58 (3 H, s, CH_3O), 3.35 (s, 3 H, CH_3O), 0.78 (3 H, d, J = 7 Hz, CH_3).

The minor isomer present for about 10% has the HCPh proton absorption at δ 4.33 (J = 6 Hz).

Hydrolysis of 13 into the β-Amino Ester 14. A solution of 0.65 g (2 mmol) of **13** in 10 mL of acetonitrile containing 0.5 g of acetic acid was kept for 30 min at room temperature. Then the solvent was evaporated in vacuo, and the remaining solid β-amino ester **14** was crystallized from diisopropyl ether: yield 90%; mp 148–149 °C; MS, m/e 315 (M + 1), 298, 284, 227, 197, 177; M^+ + 1 calcd 315.1345, found 315.1340; ^{1}H NMR δ 7.83 and 7.97 (B part of AB, 2 H, arom), 7.23 (s, 5 H, arom), 6.47 and 6.33

(17) Recently Lewis acid catalyzed reactions of silyl ketene acetals with imines have been described as stereoselective routes to β-lactams or β-amino carbonyl compounds; see, for example: Bose, A, K.; Manhas, M. S.; van der Veen, J. M.; Bari, S. S.; Wagle, D. R.; Hedge, V. R.; Krishnan, L. *Tetrahedron Lett.* **1985**, *26*, 33. Goasdoue, C.; Gaudemar, M. *Tetrahedron Lett.* **1985**, *26*, 1015.

Table I. Preparation of β-Amino Carbonyl Compounds from Imines and Enamines (Scheme III)

imine	enamine	product[a]	yield, %	mp, °C (bp, °C/mm)[b]	^{1}H NMR δ ($CDCl_3$)
1b	2a	9ba	45	131–132	9.47 (s, 1 H, HC=O), 7.33–6.30 (m, 10 H, arom), 4.43 (s, 1 H, HCPh), 4.20 (br s, 1 H, NH), 1.07 (s, 6 H, CH_3)
1b	2d	9bd	40	107	7.37–6.33 (m, 10 H, arom), 4.73 (t, 2 H, J = 7 Hz, HCPh), 4.43 (br s, 1 H, NH), 3.57 (s, 3 H, OCH_3), 2.77 (d, J = 7 Hz, CH_2)
1c	2a	9ca	50	(170/0.6)	9.47 (s, 1 H, HC=O), 7.27–6.47 (m, 5 H, arom), 4.20 (s, 1 H, HCN), 4.03 (t, J = 7 Hz, 2 H, CH_2O), 1.77–0.67 (m with two s at 1.13 and 1.20, 13 H)
1c	2c	9cc, main isomer[c]	60	68.5–69.5	7.17–6.47 (m, 5 H, arom), 4.22 (d, J = 5 Hz, 1 H, NH), 4.03 (t, J = 7 Hz, 2 H, CH_2O), 3.30–2.55 (m, 1 H, HCC=O), 2.60–0.70 (m, 16 H)
		9cc, minor isomer[c]		oil	4.43 (br s, 1 H, NH), 4.10 (t, J = 7 Hz, 2 H, CH_2O), 3.40–2.90 (m, 1 H, HCC=O)
1c	2d	9cd	60	(180/0.5)	7.30–6.50 (m, 5 H, arom), 4.43 (m, 2 H, NH and HCN), 4.10 (t, J = 6 Hz, 2 H, CH_2O), 3.67 (s, 3 H, OCH_3), 2.83 (br d, J = 5 Hz, 2 H, CH_2C=O), 0.70–1.70 (complex pattern, 7 H)
1c	2e	9ce	65	(170/0.8)	7.37–6.53 (m, 5 H, arom), 4.43 (d, J = 5 Hz, 1 H, HCN), 4.13 (t, J = 6 Hz, 2 H, CH_2=), 4.43–4.13 (NH hidden under d and t), 3.70 (s, 3 H, CH_3O), 3.30–2.77 (d of q, 1 H, $HCCH_3$), 1.73–0.70 (complex pattern with d, J = 7 Hz at 1.20, 9 H)

[a] Satisfactory analytical data (±0.4% for C, H, N were reported for the compounds listed in the table with the exception of **9ca**. The aldehyde **9ca** could not be obtained pure, and it was therefore converted into a phenylhydrazone derivative. [b] From bulb-to-bulb distillation. [c] The isomers were separated with preparative HPLC (silica gel, diisopropyl ether/hexane 1:1). They were isolated in the ratio 2:1. The main isomer was crystallized from diisopropyl ether/hexane 1:1.

(A part of AB, 2 H, arom), 4.70 (d, J = 5 Hz, 1 H, HCN), 3.87 (s, 3 H, OCH_3), 2.97 (d of q, J = 5 Hz, J = 7 Hz, 1 H, HCMe), 1.13 (d, J = 7 Hz, 3 H, CH_3).

High-Pressure Reaction of the Imine 1d[18] with the Enol Ethers 15a–e. General Procedure. A solution of 1.30 g (5 mmol) of the imine **1d** and 10 mmol of one of the enol ethers **15a–e** in 8 mL of acetonitrile was kept at a pressure of 12 kbar for 20 h at 50 °C. After release of pressure the solvent and excess of enole ether was evaporated in vacuo and diisopropyl ether was added in which the reaction products are poorly soluble. The azetidine **16da** remained as an oil: yield 85%. From ^{1}H NMR it had a purity of about 90% and the isomers were formed in the ratio 9:1. MS, m/e 360 (M + 1), 314, 288, 260. $(M^+ + 1)/e$ calcd 360.1633, found 360.1625.

^{1}H NMR (main isomer): δ 7.63 and 7.50 (B part of AB, 2 H, arom), 7.20 and 7.07 (A part of AB, 2 H, arom), 7.10 (s, 5 H, arom), 4.70 (s, 1 H, HCOEt), 4.30 (s, 1 H, HCPh), 4.12–3.27 (m, 2 H, OCH_2), 2.70 (s, 3 H, CH_3 phenyl), 1.18 (t, J = 7 Hz, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.39 (s, 3 H, CH_3). For the minor isomer the HCN proton is at 4.50 and the HCOEt proton at 4.93 ppm.

The azetidine **16db** was obtained in this way as a mixture of isomers in the ratio 8:1 (^{1}H NMR). The main isomer was obtained pure after recrystallization from diisopropyl ether: yield 70%; mp 136–138 °C; MS, m/e 329 (M + 1), 288, 260, 224. Anal. Calcd for $C_{18}H_{19}NSO_3$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.40; H, 6.21; N, 3.82.

^{1}H NMR, 90 MHz, (main isomer): δ 7.72 and 7.65 (B part of AB, 2 H, arom), 7.27–7.07 (A part of AB, 2 H, br s, 5 H, arom), 5.74 (d, J = 5 Hz, 1 H, HCO), 4.95 (d, 1 H, J = 8 Hz, HCPh), 4.13–3.60 (m, 2 H, CH_2O), 3.40–3.00 (m, 1 H, HCC), 2.40 (s, 3 H, CH_3SO_2), 1.77–1.17 (m, 2 H, CH_2). The minor isomer was not isolated. ^{1}H NMR: δ HCO, 5.37, J = 5 Hz; δ, HCPh, 4.17, J = 4 Hz.

The azetidine **16dc** was isolated as a mixture of three isomers (total yield 80%) from which the main isomer believed to be cis,cis separated as a crystalline compound after addition of diisopropyl ether: yield 35%; mp 98–99 °C; MS, m/e 358 (M + 1), 342, 314, 288, 260; ^{1}H NMR, 90 MHz, δ 7.73 and 7.63 (B part of AB, 2 H, arom), 7.40–7.06 (B part of AB and br s, 7 H, arom), 5.29 (d, J = 7 Hz, 1 H, HCOEt), 4.89 (d, J = 9 Hz, 1 H, HCPh), 4.21–3.46 (m, 2 H, OCH_2), 2.70 (d of q, 1 H, HCEt), 2.42 (s, 3 H, CH_3), 1.21 (t, J = 7 Hz, 3 H, CH_3, OEt), 1.21–1.00 (m, 2 H, $-CH_2$, Et), 0.55 (t, J = 7 Hz, 3 H, CH_3, Et). Anal. Calcd for $C_{20}H_{23}NSO_3$: C, 67.22; H, 6.44; N, 3.92. Found: C, 66.76; H, 7.03; N, 3.94.

The remaining solution in diisopropyl ether contained three isomers of **16dc** which could be separated by preparative HPLC (silica gel, diisopropyl ether/hexane 3:1), yielding the three isomers cis,cis, trans,cis, and cis,trans in the ratio 2:5:6. The isomer indicated as trans,cis gave the corresponding mass spectrum as the cis,cis isomer of **16dc**: $(M^+ + 1)/e$ calcd 358.1477, found 358.1480. ^{1}H NMR, 90 MHz, δ 7.74 and 7.64 (B part of AB, 2 H, arom), 7.21 and 7.11 (A part of AB, 2 H, arom), 7.37 (s, 5 H, phenyl), 5.23 (d, J = 3 Hz, 1 H, HCOEt), 5.17 (d, J = 9 Hz, 1 H, HCPh), 4.22–3.44 (m, 2 H, CH_2O), 2.50–2.30 (m, 1 H, HCEt), 2.40 (s, 3 H, CH_3SO_2), 1.20 (t, J = 7 Hz, 3 H, CH_3, OEt), 0.64 (t, J = 7 Hz, 3 H, CH_3, Et).

The isomer **16dc** indicated as cis,trans had the same mass spectrum as the cis,cis and trans,cis isomers: $(M^+ + 1)/e$ calcd 358.1477, found 358.1484. ^{1}H NMR: δ 7.66 and 7.53 (B part of AB, 2 H, arom), 7.23 and 7.10 (A part of AB, 2 H, arom), 4.90 (d, J = 5 Hz, 1 H, HCOEt), 4.20 (d, J = 7 Hz, 1 H, HCPh), 3.97–3.33 (m, 2 H, CH_2O), 2.35 (s, 3 H, CH_3SO_2), 2.30–2.00 (m, 1 H, HCEt), 1.21 (t, J = 7 Hz, 3 H, CH_3), 0.78 (t, J = 7 Hz, 3 H, CH_3).

The open product **18dd** crystallized after addition of diisopropyl ether. It was recrystallized from THF: mp 147–149 °C; yield 70%; MS, m/e 346 (M + 1), 288, 260, 175; ^{1}H NMR δ 7.50 and 7.37 (B part of AB, 2 H arom), 7.05 and 6.93 (A part of A, 2 H, arom), 7.03 (s, 5 H, phenyl), 5.33 (br d, J = 5 Hz, 1 H, NH), 4.63–4.20 (m, 1 H, HCPh), 3.73 (br s, 2 H, H_2C=C), 3.50 (q, 1 H, CH_2O), 3.47 (q, 1 H, CH_2O), 2.33 (d, J = 7 Hz, 2 H, CH_2C=C), 2.30 (s, 3 H, CH_3SO_2), 1.17 (t, J = 7 Hz, 3 H). Anal. Calcd for $C_{19}H_{23}NSO_3$: C, 66.06; H, 6.71; N, 4.05. Found: C, 66.56; H, 6.95; N, 4.06.

Hydrolysis of the Azetidines 16da and 16dc, Cis,cis, Trans,cis, Cis,trans into the Aldehydes 17da and 17dc, Erythro and Threo. General Procedure. To a solution of 200 mg of the azetidines in 10 mL of acetonitrile was added 0.5 mL of H_2O and 0.2 g of acetic acid. The mixture was kept for 30 min at room temperature, and after that the solvent was evaporated in vacuo. The 50 mL of chloroform was added, and the organic solution was washed several times with water and after that dried over Na_2SO_4. Evaporation of the solvent in vacuo left the aldehydes in yields of more than 90% and with a purity of at least 90%.

The aldehyde **17da** was further purified by crystallization from diisopropyl ether/acetonitrile: mp 163 °C; MS, m/e 332 (M + 1), 288, 260, 172; ^{1}H NMR δ 9.43 (s, 1 H, HCO), 7.40 and 7.27 (B part of AB, 2 H, arom), 6.97 (br s, 5 H, phenyl), 6.93 and 6.80 (A part of AB, 2 H, arom), 6.07 (d, J = 10 Hz, 1 H, NH), 4.43 (d, J = 10 Hz, 1 H, HCPh), 2.27 (s, 3 H, CH_3SO_2), 1.00 (s, 6 H, CH_3). Anal. Calcd for $C_{18}H_{21}NSO_3$: C, 65.23; H, 6.39; N, 4.23. Found: C, 64.75; H, 6.54; N, 4.24.

The aldehyde **17dc** (erythro) was obtained as well from the azetidine **16dc** cis,cis as from **16dc** trans,cis: yield 90%; mp 105.5–107.5 °C after crystallization from diisopropyl ether. MS, m/e 332 (M + 1), 288, 260, 172. ^{1}H NMR: δ 9.40 (d, J = 2.5 Hz,

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1 H, HCO), 7.50 and 7.37 (B part of AB, 2 H, arom), 7.03 and 6.90 (A part of AB, 2 H, arom), 7.00 (s, 5 H, phenyl), 6.03 (d, J = 9 Hz, 1 H, NH), 4.60 (d of d, J = 9 Hz, J = 7 Hz, 1 H, HCPh), 2.83-2.40 (m, 1 H, HCEt), 2.40 (s, 3 H, CH_3SO_2), 1.97-1.47 (m, 2 H, CH_2), 0.87 (t, 3 H, J = 7 Hz, CH_3). Anal. Calcd for $C_{18}H_{21}NSO_3$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.11; H, 6.17; N, 4.22.

The aldehyde **17dc** (threo) was obtained as an oil from the azetidine **16dc** cis,trans. Because the azetidine could not be obtained completely pure, the aldehyde was contaminated with about 5% of the erythro aldehyde. The mass spectrum showed the same peaks as for the erythro aldehyde. Typical peaks in the ^{1}H NMR are δ 9.57 (d, J = 4 Hz, 1 H, HC=O), 4.57 (d, J = 8 Hz, 1 H, HCPh after addition of p-toluenesulfonic acid).

C(2)-Functionalized Tryptophans from 3-Acetoxyindoles and Their Possible Implication in Indole Alkaloid Biosynthesis†

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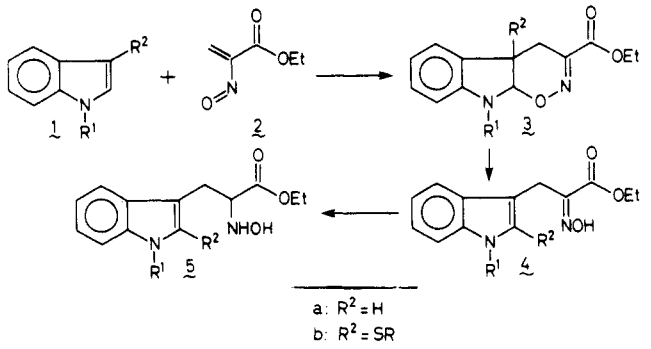
The acetoxyindoles **10** and **11** are efficiently converted (85-95%) into the dihydro-1,2-oxazines **13** and **14**, respectively, by reaction with the transient nitroso olefin **2**, prepared in situ from ethyl α-(hydroxyimino)-β-bromopropanoate by base treatment. The cycloadducts **13** and **14** react efficiently with thiols or a hydride donor to yield (60-90%) the 2-substituted tryptophan derivatives **9a-f**. Selective reduction of the oxime function of the 2-(*S*-cysteinyl)tryptophan derivative **9d** afforded **19**, a derivative of tryptathionine. The sulfonium salt **22b** derived from 2-(ethylthio)tryptophan derivative **9b** was shown to undergo a thio-Claisen rearrangement to yield **26**. This reaction supports Bycroft's proposal involving a thio-Claisen rearrangement in indole alkaloid biosynthesis.

Introduction

The biogenetic relationship between tryptophan and α-substituted, α,β-disubstituted, or α,β-dehydro tryptophans has been suggested to proceed via *N*-hydroxytryptophan derivatives.[1] This postulate is supported by the biosynthetic pathway to glucosinolates derived from tryptophan (e.g., glucobrassicins[2a]) which proceeds via *N*-hydroxytryptophan[2b,c] and by the recent isolation of astechrome[3] and the eudistomins,[4] natural products having *N*-hydroxytryptophan—or a derivative thereof—as a characteristic structural element. We have shown, moreover, that *N*-hydroxytryptophan deserves attention not only as a biosynthetic precursor, but also as a synthon for natural products featuring tryptophan derivatives.[1,5]

One of the approaches we explored successfully for the synthesis of *N*-hydroxytryptophan **5** and related compounds starts with the cycloaddition of the nitroso olefin **2** to the C(2)-C(3) double bond of indol (**1a**) to yield **3a** (Scheme I). Base-catalyzed ring opening and rearomatization afforded **4a**.[1] As part of a further exploration of this reaction we observed recently[6] that the cycloaddition of **2** to 3-(alkylthio)indoles **1b** gave **4b** in which the alkylthio group had migrated from C(3) to C(2). This rearrangement occurs with good yields under mild conditions (room temperature, CH_2Cl_2, Na_2CO_3) and is rationalized as represented in Scheme II. The indolenine **6b**, being in equilibrium with **3b**, might form the episulfonium ion **7** which yields **4b** by rearomatization. The cycloadducts **3a** and **3b** appeared to be unstable intermediates, which escaped isolation. We became intrigued by the potential usefulness of a stable derivative of cycloadduct **3**. We reasoned that if substituent R^2 has a low migratory aptitude, **3** might be an isolable compound that might react with external nucleophiles as depicted in Scheme II, sequence **3** → **6** → **8** → **9**. Here we report that this approach

Scheme I



is viable. Cycloadduct **3** can be isolated indeed when R^2 is an acetoxy group. Treatment with nucleophiles yields **9**, a reaction for which we propose **8** as an intermediate.

Results

The 3-acetoxyindoles **10-12** (Scheme III) were prepared according to literature procedures.[7] Reaction of **11** with **2**—prepared in situ by treatment of ethyl α-(hydroxyimino-β-bromopropanoate[1,8] with Na_2CO_3—afforded regio- and stereospecifically the desired dihydro-1,2-oxazino-

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