In Situ Preparation and Subsequent Use of Isomerically Pure *E*- and *Z*-Crotylamines in a 3-Aza-Claisen Rearrangement

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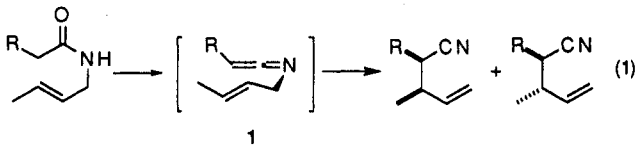
As part of an ongoing study of an extremely mild 3-aza-Claisen rearrangement developed in our laboratory,[1] we desired to probe the stereochemical consequences of a transformation which most likely proceeds *via* a 3-aza-1, 2, 5-hexatriene intermediate (1) as shown in eq 1.[2] In order to best compare the acyclic stereocontrol of this reaction relative to that of related sigmatropic processes,[3] a synthesis of the isomerically-pure crotylamines was highly desirable.[4]

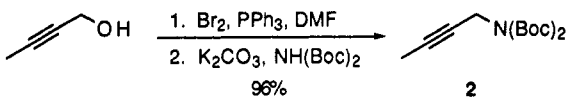


(1)

1

Due to the importance of allylic amines in the synthesis of natural products, a number of procedures aimed at their preparation have been developed.[5] Some recent examples include direct displacement of allylic leaving-groups with nitrogen nucleophiles,[6] metal-assisted aminations,[7] and Wittig olefinations.[8] Although many of these methods are highly stereoselective with respect to the alkene isomer produced, none of them address the challenge of producing both crotylamine isomers. With the limitations of these procedures in mind, we envisioned a divergent approach to the desired compounds which would involve the stereoselective reduction of a suitably protected butynylamine. This tactic, used effectively in the preparation of *E*- and *Z*-crotyl alcohols,[9] appeared not to have been applied to the problem at hand. Herein we report the successful *in situ* preparation of isomerically pure (>95%) *E*- and *Z*-crotylamines from 2-butyn-1-ol, their conversion to their respective phenylacetamide derivatives, and the stereochemical outcome of the rearrangement of these isomerically pure *N*-crotyl amides.

Scheme 1



2

The key protected alkynyl amine **2** was readily obtained from the corresponding alcohol. In a one-pot procedure, 2-butyn-1-ol was treated with Ph_3P/Br_2 in DMF,[10] followed by $HN(Boc)_2$[11] and K_2CO_3, leading to the desired butynylamine in 96% yield (Scheme 1).[12,13] The *tert*-butoxycarbonyl (Boc) group was chosen as ideal for N-protection because it offered stability to our chosen methods for olefin reduction and could easily be removed under mild, acidic conditions.

Reduction of the alkyne using the conditions of Tour[14] gave a moderate (41% isolated) yield of the pure *Z*-isomer (Scheme 2). A improved approach was found in the reduction of the alkyne with H_2/Lindlar which gave the same isomer **3** in a favorable 91% yield.[15] Reduction of **2** to the *Z*-isomer was best accomplished when one Boc group was removed with TFA prior to treatment with Na/NH_3.[9a] This procedure gave the protected *E*-crotylamine **4** in 89% yield over two steps.

These protected crotylamines were deprotected *in situ* (TFA/CH_2Cl_2)[7a] and then directly converted into the phenylacetamide isomers **5** and **6** (in unoptimized yields of 62 and 54%, respectively) by reaction with phenylacetyl chloride/Et_3N.

Each of the pure isomers was then subjected to one of the rearrangement protocols we have developed. Use of $I_2/(EtO)_3P/Et_3N$[1b] led to a 1.1:1 ratio of diastereomers in the case of **5** while **6** gave the same major isomer, reproducibly, in a slightly improved ratio of 1.6:1 (^1H NMR integration).[16]

We have developed an *in situ* preparation of *E*- and *Z*-crotylamine to enable us to investigate the extent of diastereocontrol inherent in a six-atom transition state which includes a linear ketenimine. This procedure should allow us to prepare the corresponding *E*- and *Z*-2-butenylpropanamides, the rearrangement products of

(1) Walters, M. A.; McDonough, C. S.; Brown, P. S., Jr.; Hoem, A. B. *Tetrahedron Lett.* **1991**, *32*, 179. (b) Walters, M. A.; Hoem, A. B.; Arcand, H. R.; Hegeman, A. D.; McDonough, C. S. *Tetrahedron Lett.* **1993**, *34*, 1453.

(2) Excellent diastereoselectivity (10:1) has been reported by Molina for one example of this reaction, while Nubbemeyer has observed a lack of 1,2-stereocontrol for this process in his recent work directed toward the synthesis of optically active γ-butyrolactones. See: (a) Molina, P.; Alajarin, M.; Lopez-Leonardo, C.; Alcantara, J. *Tetrahedron* **1993**, 5153. (b) Nubbemeyer, U. *Synthesis* **1993**, 1120.

(3) For example, the ester-enolate Claisen is known to proceed with good diastereoselectivity. See: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572. (d) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896. (e) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

(4) For a preparation of the pure *E*-isomer see: Corriu, R. J. P.; Bolin, G.; Moreau, J. J. E. *Tetrahedron Lett.* **1991**, *32*, 4121.

(5) Cheikh, R. B.; Chaabouni, R. *Synthesis* **1983**, 685.

(6) (a) Bestmann, H. J.; Wölfel, G. *Chem. Ber.* **1984**, *117*, 1250. Yamamoto, Y.; Asao, N. *J. Org. Chem.* **1990**, *55*, 5303. (b) Murai, T.; Yamamoto, M.; Kato, S. *J. Chem. Soc., Chem. Commun.* **1990**, 789. (c) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675.

(7) (a) Connell, R. D.; Rein, T.; Akermark, B.; Helquist, P. A. *J. Org. Chem.* **1988**, *53*, 3845. (b) Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292. (c) Nayyar, N. K.; Reddy, M. M.; Iqbal, J. *Tetrahedron Lett.* **1991**, *32*, 6965. (d) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.

(8) (a) Saari, W. S.; Fisher, T. E. *Synthesis* **1990**, 453. (b) Dellaria, J. F., Jr.; Sallin, K. J. *Tetrahedron Lett.* **1990**, *31*, 2661.

(9) For examples see: (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (b) Cohen, N.; Eichel, W.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3512.

(10) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.

(11) $NH(Boc)_2$ is now commercially available. For a simple synthesis of this reagent see: Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275.

(12) (a) Arcadi, A.; Bernocchi, E.; Cacchi, S.; Caglioti, L.; Marinelli, F. *Tetrahedron Lett.* **1990**, *31*, 2463. (b) Van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6083.

(13) Our attempts to use the iminodicarbonate $NH(Boc)_2$ with standard Mitsunobu conditions failed. (a) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (b) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L.; U., R. *J. Org. Chem.* **1991**, *56*, 7172. However, for a successful application of this methodology in the preparation of allylic amines see ref 6c.

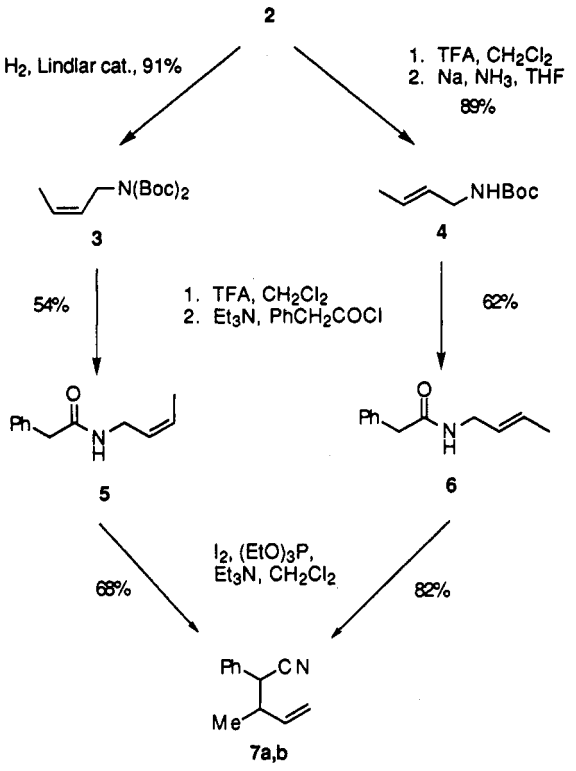
(14) Tour, J. M.; Cooper, J. P.; Pendalwar, S. L. *J. Org. Chem.* **1990**, *55*, 3452.

(15) Lindlar, H.; Dubois, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol V, p 880.

(16) Overnight treatment of the different mixtures of product nitriles **7a,b** with Et_3N in CH_2Cl_2 did not change the ratio of either mixture.

0022-3263/94/1959-2645$04.50/0

Scheme 2



which we will attempt to correlate with the products arising from the analogous ester-enolate Claisen reactions. Studies along these lines are currently in progress in our laboratories and will be reported shortly.

Experimental Section

Unless otherwise noted, all nonaqueous reactions were carried out under a dry argon atmosphere with flame-dried glassware. Ether and THF were distilled from sodium/benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. Triethylamine (Et_3N) was distilled and stored over potassium hydroxide. DMF was dried over activated 4-Å molecular sieves. TLC was performed on glass-backed silica plates (60 F-254, thickness = 0.25 mm, eluent was usually a mixture of ethyl acetate (EtOAc)/hexanes) and was used to monitor reactions. The TLC plates were visualized under UV light or developed with a $KMnO_4$ (6 g of $KMnO_4$, 10 mL of 5% NaOH, 40 g of K_2CO_3, diluted with H_2O to 1 l) or *p*-anisaldehyde (7.5 mL of *p*-anisaldehyde, 3.5 mL concd H_2SO_4, 1.5 mL of glacial acetic acid, and 135 mL of 95% EtOH) spray reagent. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory, Inc.

1-[Bis(*tert*-butoxycarbonyl)amino]-2-butyne (2). A solution of 1.84 g (7.02 mmol) of triphenylphosphine in 9.5 mL of dry DMF was cooled to 0 °C. To this stirred solution was added slowly, *via* syringe, 0.36 mL (7.02 mmol) of bromine, until the bromine color remained. When about 0.25 mL of bromine had been added, 0.10 mL of 2-butyn-1-ol was added, *via* syringe, to maintain homogeneity. The maroon solution was stirred for 5 min before the remaining 0.40 mL (0.50 mL total, 6.67 mmol) of 2-butyn-1-ol was added *via* syringe. After warming to room temperature and stirring for 2.5 h, this solution was treated with 2.31 g (16.7 mmol) of K_2CO_3. After an additional 20 min, 0.974 g (4.48 mmol) of $NH(Boc)_2$ was added to the reaction. The resulting creamy solution was stirred for 36 h before being partitioned between water and ether, and the aqueous phase was extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an impure yellow solid. Chromatography of the residue on silica gel (eluent 10% EtOAc/hexane) gave 1.16 g (96%) of **2** isolated as a slightly yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (q, J = 2.4 Hz, 2H), 1.78 (t, J = 2.4 Hz, 3H) 1.50 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 82.4, 77.9, 74.7, 36.0, 27.8, 3.3; IR (neat) 1789, 1751 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.36; H, 8.56; N, 5.47.

1-[Bis(*tert*-butoxycarbonyl)amino]-2(*Z*)-butene (3).[7a] Two methods were developed for the preparation of **3**.

Method A: A stirred solution of 0.226 g (0.838 mmol) of **2**, 0.008 mL (0.067 mmol) of quinoline, and 0.032 g of Lindlar catalyst was placed under an H_2 atmosphere. The H_2 was generated by adding a pellet of cobalt-doped $NaBH_4$ to water in a separate flask. This flask was equipped with a balloon and a drying tube that connected the reaction flask with the $NaBH_4$/water solution. After 3 h, the reaction was filtered through a plug of silica gel and concentrated *in vacuo*. Chromatography of the residue (eluent 5% EtOAc/hexane) gave 0.207 g (91%) of **3** as a clear oil.

Method B: To a solution of 0.565 g (2.10 mmol) of **2** and 0.071 g (0.32 mmol) of $Pd(OAc)_2$ in 21 mL of a 5:1 mixute of THF/water was added *via* syringe 0.426 mL (2.31 mmol) of triethoxysilane. After stirring for 2.5 h, the solution was filtered through a plug of silica gel, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel (eluent 5% EtOAc/hexane) gave 0.235 g (41%) of **3** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (m, 1H), 5.40 (m, 1H), 4.21 (d, 2H), 1.68 (d, 3H), 1.48 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 126.5, 126.3, 82.0, 43.1, 28.0, 13.0.

1-[(*tert*-Butoxycarbonyl)amino]-2(*E*)-butene (4). To a solution of 0.862 g (3.20 mmol) of **2** in 32 mL of CH_2Cl_2 was added 0.20 mL (3.47 mmol) of TFA. This solution was stirred for 2 h and was concentrated *in vacuo*. The residue was dissolved in 10 mL of freshly distilled THF and transferred, *via* cannula, to approximately 53 mL of liquid ammonia cooled to −78 °C. This solution was treated with 0.450 g (19.9 mmol) of Na. Once the solution turned blue, it was stirred for an additional 5 min before it was quenched with solid NH_4Cl. The ammonia was allowed to evaporate overnight and the resultant residue was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 0.486 g (89%) of **4** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.33–5.65 (m, 2H), 4.64 (bs, 1H), 3.59 (bt, 2H), 1.61 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 127.5, 127.4, 79.0, 42.4, 28.3, 27.9, 17.5; IR (neat) 3346, 1694 cm^{-1}.

***N*-[(*Z*)-2-Butenyl]phenylacetamide (5).** To a solution of 0.197 g (0.724 mmol) of **3** in 2.9 mL of dry CH_2Cl_2 was added 1.0 mL of TFA. After stirring overnight, the solution was concentrated *in vacuo*. The residue was dissolved in 2.9 mL of dry CH_2Cl_2 and treated, *via* syringe, with 0.61 mL (4.34 mmol) of Et_3N. After stirring the reaction for 5 min, 0.105 mL (0.796 mmol) of phenylacetyl chloride was added *via* syringe. The solution was stirred for 1 h before being partitioned between water and ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the residue on silica gel (eluent 25% EtOAc/hexane) gave 73.5 mg (54%) of **5** as a solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.40 (m, 5H), 5.43–5.65 (m, 2H), 5.21–5.39 (m, 1H), 3.86 (t, J = 6.0 Hz, 2H), 3.56 (s, 2H), 1.61 (compd, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 134.9, 129.3, 128.9, 127.7, 127.2, 125.8, 43.6, 36.5, 12.9; IR (CH_2Cl_2) 3432, 1668 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_1$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.91; H, 7.74; N, 7.12.

***N*-[(*E*)-2-Butenyl]phenylacetamide (6).** The same procedure was used as for the preparation of **5**. 0.122 g (0.713 mmol) of **4** in 2.8 mL of dry CH_2Cl_2 with 0.65 mL of TFA and then 2.8 mL of dry CH_2Cl_2 with 0.60 mL (4.28 mmol) of Et_3N and 0.10 mL (0.78 mmol) of phenylacetyl chloride gave 83.6 mg (62%) of **6** of a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.21–7.40 (m, 5H), 5.30–5.61 (m, 3H), 3.76 (t, J = 6.0 Hz, 2H), 3.57 (s, 2H), 1.64 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 134.9, 129.4, 128.9, 128.1, 127.2, 126.6, 43.7, 41.4, 17.6; IR (CH_2Cl_2) 3432, 1667 cm^{-1}.

Typical Procedure for the Formation of 3-Methyl-2-phenyl-4-pentenenitrile (7a,b). Rearrangement of Amide 5. A solution of 0.173 g (0.68 mmol) of iodine in 0.4 mL of CH_2Cl_2 was titrated (*via* syringe) with triethyl phosphite (0.120 mL, 0.70 mmol) until the solution was colorless. This solution was transferred, *via* cannula, to a solution of 0.0430 g (0.227 mmol) of amide **5** in 0.5 mL of CH_2Cl_2. After stirring for 5 min, the

solution was treated with 0.095 mL (0.68 mmol, 3.0 equiv) of Et_3N. This reaction was stirred for 30 min before being partioned between water and ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography of the residue on silica gel (eluent 10% EtOAc/hexane) gave 26.5 mg (68%) of a mixture of nitriles **7a** and **7b** as a clear oil. Isomer ratios of the nitrile products, as determined by ^1H NMR, from the peaks at δ 3.83 and 3.74, was 1.1:1. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16–7.39 (m, 5H), 5.61–5.81 (m, 1H), 4.96–5.12 (m, 2H), 3.83 (d, J = 6.0 Hz, 1H), 2.63–2.71 (m, 1H), 1.06 (d, J = 6.3 Hz, 3H). Minor isomer: ^1H NMR peaks that are distinguishable include 3.74 (d, J = 6.6 Hz, 1H) and 1.08 (d, J = 6.3 Hz, 3H). Mixture of isomers: ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.8, 134.1, 128.8, 128.2, 128.0, 119.6, 119.4, 117.2, 116.4, 44.0, 43.7, 42.7, 42.3, 18.0, 15.9; IR (neat) 2240 cm^{-1}; MS m/z (rel inten) 171 (M^+, 2), 117 (100), 89 (24), 55 (29).

Rearrangement of Amide 6. Following the above procedure with 0.0645 g (0.341 mmol) of amide **6**, 0.249 g (1.02 mmol) of iodine, 0.177 mL (1.06 mmol) of triethyl phosphite, and 0.143 mL (1.02 mmol) of Et_3N in 0.9 mL of CH_2Cl_2 gave 47.6 mg (82%) of nitriles **7a** and **7b** in a 1.6:1 ratio of diastereomers.

Acknowledgment. Acknowledgement is made to Dartmouth College and to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for the support of this work.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of compounds **4**, **6**, and **7a,b** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.