Tetrahedron Letters, Vol. 34, No. 4, pp. 579-582, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

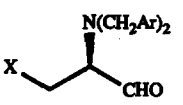
A Novel Dyatropic Rearrangement of γ-N,N-Dibenzylamino α,β-Dehydro N-Formylamino Acid Esters

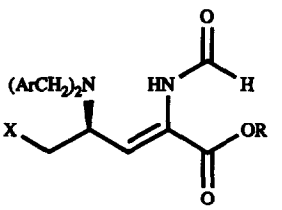
Andrew S. Kende*, K. M. J. Brands, and Benjamin Blass

Department of Chemistry, University of Rochester, Rochester, New York 14627, USA

Abstract: *γ-N,N-Dibenzylamino α,β-dehydro N-formylamino acid esters of type 2 undergo a dyatropic thermal rearrangement in refluxing toluene to yield the isomeric urea derivatives 3. Evidence for a dissociation-recombination mechanism is presented.*

Enantiopure N-formylenamine esters of structure **2** are readily available from amino acids and can serve as chiral pool-derived dienophiles for certain highly stereoselective cycloaddition reactions.[1] Specifically, D-(-)-alanine may be converted by a literature procedure to aldehyde **1a**,[2] which reacts by the Schöllkopf isonitrile procedure[1,3] to give ca. 60% of the crystalline Z-enamide **2a**, mp 111 °C, plus ca. 30% of the liquid E-isomer. Alternatively, the D-(-)-serine-derived aldehyde **1b** reacts with MeO_2CCH_2NC employing Cu_2O-catalysis,[4] followed by oxazoline hydrolysis (aq. HOAc-THF, 20 °C, 16 h) and stepwise β-elimination ($MsCl/Et_3N$, 0 °C to 20 °C, then DBU/CH_2Cl_2 at reflux) to give as major product the Z-enamide **2b**, mp 86-87 °C, in ca. 66% yield.

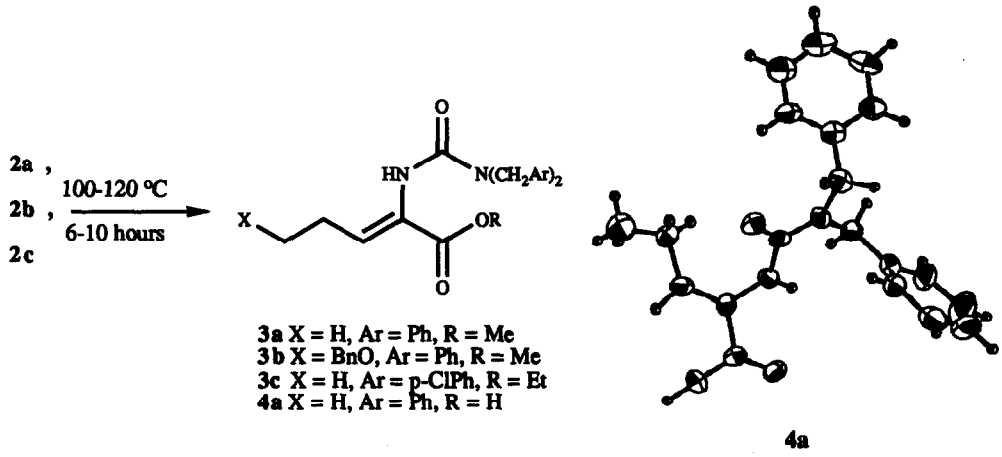




1a X = H, Ar = Ph
1b X = BnO, Ar = Ph
1c X = H, Ar = p-ClPh

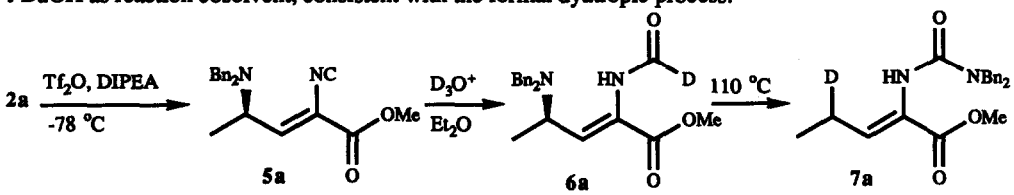
2a X = H, Ar = Ph, R = Me
2b X = BnO, Ar = Ph, R = Me
2c X = H, Ar = p-ClPh, R = Et

We now report that the enamide ester **2a** undergoes an unprecedented rearrangement at 100-120 °C in inert organic solvents. Thus a solution of **2a** in toluene at reflux for 6-12 h leads in 80-85% yield to a single new crystalline reaction product, mp 62-63 °C, isomeric with **2a**. The IR, ^{1}H-NMR, ^{13}C-NMR and FDMS spectra of this new compound are in full accord with the unsaturated urea structure **3a**,[5] although they do not establish its double bond stereochemistry. The serine-derived Z-enamide **2b** undergoes analogous thermal rearrangement to produce urea derivative **3b**. Under the above reaction conditions, the E-isomer of **2a** is largely decomposed, and only traces of **3a** are detected. Hydrolysis of the ester function in **3a** (aq. LiOH-MeOH/THF, 20 °C, 2 h) gives in 59% yield the crystalline acid **4a**, mp 126-127 °C, which with CH_2N_2 is cleanly reconverted to ester **3a**. A single-crystal X-ray structure determination of acid **4a** gave the stereoformula shown,[6] thereby establishing the stereospecificity of the thermal rearrangement (Z-**2a** → Z-**3a**).



4a

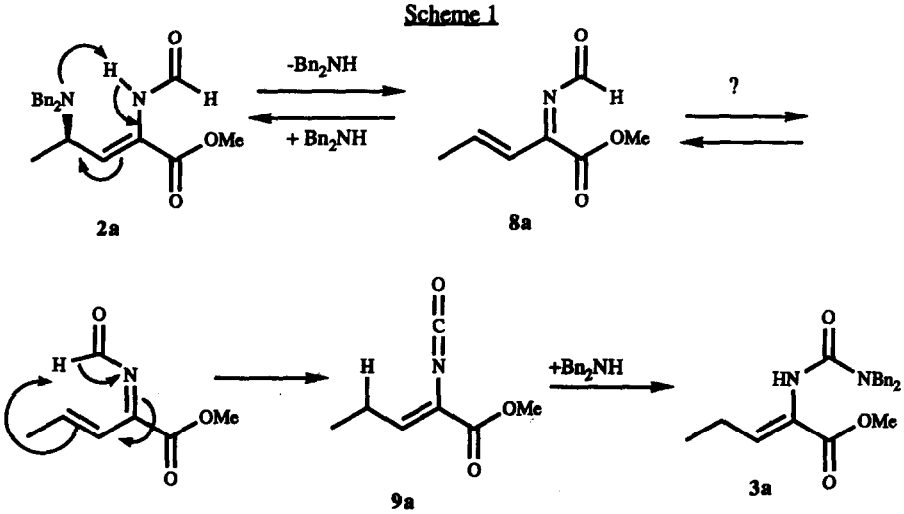
The high-yield thermal isomerization of enamide esters **2** to the corresponding urea esters **3** is a new dyatropic rearrangement[7] in which 1,5-migration of a dibenzylamino group from saturated carbon is accompanied by apparent 1,5-migration of formyl hydrogen in the reverse direction! The postulated 1,5-migration of formyl hydrogen has been experimentally confirmed as follows: Dehydration of **2a** (Tf_2O, iPr_2NEt-CH_2Cl_2, -78 °C, 15 min, 99% yield)[8] gave isonitrile **5a**. This was "rehydrated" (DCl in D_2O-Et_2O, 20 °C, 2 h, 71% yield) to give the deuterated enamide **6a**. Pure **6a** underwent thermal isomerization in refluxing toluene to yield the C-4 monodeuterated product **7a**; the same **7a** was produced in the presence of t-BuOH as reaction cosolvent, consistent with the formal dyatropic process.



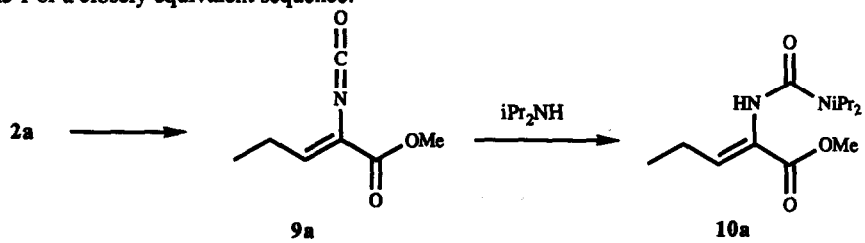
We find that the transformations of either **2a** or **2c** to **3a** or **3c**, respectively, proceed at comparable rates and yields in the presence or absence of O_2, in the dark or in light, and in benzene, toluene, t-BuOH or n-PrOH as solvent or cosolvent. The reaction of **2c** in toluene is, however, diverted by addition of one equiv. of either Ac_2O or 1-naphthyl isocyanate. Under these conditions, no **3c** is formed, and the byproducts $CH_3CON(p\text{-}ClBn)_2$ or 1-NpNHCON(p-ClBn)$_2$, respectively, are produced in good yields. To test the possibility that a dissociation-recombination mechanism involving free Bn_2NH may be involved in the rearrangement, certain foreign secondary amines (e.g., PhNHMe, BnNHMe) were added to the rearrangement solvents. Unfortunately, these amines substantially destroyed the reactant **2a**, probably by N-deformylation (vide infra). Therefore, a crossover experiment was carried out. Pure $(p\text{-}ClC_6H_4CH_2)_2N$-substituted *ethyl* ester **2c**, shown independently to rearrange in good yield to urea **3c**, was mixed with equimolar *methyl* ester **2a**, and the mixture refluxed in toluene. Careful FDMS analysis of the combined urea products, using all appropriate controls,[9] showed the equal formation of all four possible products resulting from essentially complete crossover of the -NR_2 groups with respect to the two ester frameworks.

A rearrangement mechanism consistent with our data is pictured in Scheme 1. The rearrangement would proceed by an initial syn-elimination of $HNBn_2$ from **2a** to yield acylimine **8a**. Possible syn-anti N-formyl isomerization[10] and subsequent 1,5-migration of hydrogen would produce the unsaturated isocyanate **9a**, and readdition of $HNBn_2$ would yield the observed urea **3a**. Although the failure of n-PrOH as solvent to shut down the rearrangement would seem to preclude an isocyanate intermediate, a control run with 1-naphthyl isocyanate seems to suggest otherwise. Specifically, when 1-naphthyl isocyanate (1 equiv.) is stirred with 10,000 equiv. of MeOH containing 2 equiv. of Bn_2NH, the only product detected was 1-NpNHCONHBn2; no 1-NpNHCO2Me was observed!

Scheme 1



More direct evidence was obtained from ^{1}H-NMR kinetic runs on the rearrangement of **2a** in C_6D_6. Conversion of **2a** to **3a** showed an apparent induction period over the first quarter of a half-life, followed thereafter by observed first-order kinetics for the formation of **3a**. Careful ^{1}H-NMR monitoring of the reaction during the "induction period" showed the development of a new set of weak but distinct proton signals (δ 1.89, quintet; 6.09, triplet) different from **3a** but consistent with the postulated isocyanate **9a**. An IR scan of this sample showed a sharp medium-intensity peak at 2220 cm^{-1} (*cf.* 1-NpNCO in C_6D_6, ν = 2220 cm^{-1}). Both the IR peak and the ^{1}H-NMR signals for **9a** disappeared rapidly on addition of iPr_2NH to this sample; subsequent chromatography of this spiked sample led to the isolation of **10a**, fully characterized by IR, ^{1}H-NMR and its EI mass spectrum. Thus, the appearance of isocyanate **9a**, initially rising during the first quarter of a half-life, then slowly declining as the reaction progresses, is consistent with the mechanism of Scheme 1 or a closely equivalent sequence.[11]



Although there is negligible appearance of product **3a** during the initial "induction period," no free Bn_2NH is seen in the ^1H-NMR. However, during this period, weak new signals for a byproduct derived from Bn_2NH can be observed by ^1H-NMR. This byproduct has been identified by chromatographic isolation and EIMS as Bn_2NCHO. We conclude that in these early stages some Bn_2NH is indeed generated, but reacts in a minor side reaction by formyl transfer to give Bn_2NCHO. As soon as the steady-state concentration of isocyanate **9a** becomes significant, subsequent Bn_2NH predominantly reacts with **9a** to produce the major product **3a** as in Scheme 1.

We have shown that the novel dyatropic rearrangement of **2a** to **3a** most likely proceeds by a dissociation-recombination mechanism through an isocyanate intermediate as suggested in Scheme 1. While the details and scope of this type of rearrangement remain to be established, Scheme 1 pictures certain intermediates which may offer synthetically fruitful chemistry.[12] The synthetic implications of this new reaction pathway are under exploration.

Acknowledgment. Partial support of this research by grant CA 18846, awarded by the National Cancer Institute (NIH), is gratefully acknowledged. B.B. thanks the University of Rochester for a Sherman Clarke Fellowship.

References and Notes

1 Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453. The Z-stereochemistry of series 2 is proven in this reference, and that of **2b** independently confirmed by us through an X-ray of a Diels-Alder derivative.

2 Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.

3 Schöllkopf, U.; Gerhart, F.; Schröder, R.; Hoppe, D. *Liebigs Ann. Chem.* **1972**, *766*, 116.

4 Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316.

5 Compound **3a**: ^1H-NMR (300 MHz, $CDCl_3$): δ 7.40-7.26 (10H, m), 6.49 (1H, t), 5.91 (1H, s), 4.58 (4H, s), 3.72 (3H, s), 2.06 (2H, quintet), 1.00 (3H, t). ^{13}C-NMR ($CDCl_3$): δ 165.8, 156.1, 137.7, 137.0, 128.7, 128.5, 127.5, 127.1, 52.0, 50.4, 21.4, 12.7. IR ($CHCl_3$): 1725, 1675 cm^{-1}. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.55; H, 6.87. Found: C, 71.90; H, 6.75.

6 We are grateful to Mr. G. Rosini and Mr. A. Selmeczy of this department for their help in the X-ray analysis, which was carried out on an Enraf-Nonius 586 CAD4 diffractometer; R = .075 for structure **4a**.

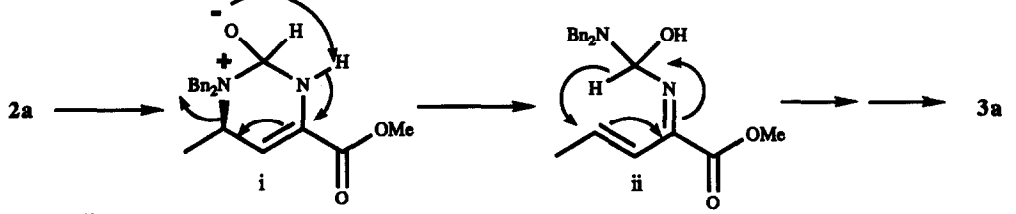
7 A dyatropic rearrangement is one in which two migrating groups or atoms exchange places; *cf.* Reetz, M. T. *Chem. Ber.* **1977**, *110*, 954.

8 Baldwin, J. E.; O'Neil, I. A. *Syn. Lett.* **1990**, *8*, 603.

9 Control runs showed that clean molecular ions could be observed for FDMS of pure **2a**, **2c**, **3a**, and **3c**. Exposure of a mixture of pure products **3a** and **3c** to 12 h reflux in toluene did not lead to any crossover. We are grateful to Mr. C. J. Wright and Mr. T. R. Criswell, Eastman Kodak Research Laboratories, for the FDMS determinations.

10 For salient references to thermal imine isomerizations, see Padwa, A. *Chem. Rev.* **1977**, *77*, 37.

11 An alternative to Scheme 1 would assume intramolecular attack by Bn_2N- nitrogen on the formyl carbonyl (**2a** → i) followed by a β-elimination step to give an aminal (i → ii). Subsequent 1,5-hydrogen shift would yield the observed urea (ii → **3a**). Such a formulation would not demand an isocyanate intermediate, nor provide an attractive explanation for the complete crossover observed for the products.



12 *Cf.* Effenberger, F.; Baumgartner, C.; Kühlwein, J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1053, and references therein.

(Received in USA 23 September 1992)