Tetrahedron Letters, Vol.22, No.41, pp 4097 - 4100, 1981
Printed in Great Britain

0040-4039/81/414097-04$02.00/0

STEREOCONTROLLED SYNTHESIS OF CONJUGATED DIENAMIDES VIA THE YNAMINE-CLAISEN REARRANGEMENT WITH (ARYLTHIO)YNAMINE [1)]

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SUMMARY: *A new, versatile method for the stereocontrolled synthesis of conjugated (E, E)-dienamides is described which relies upon the acid-catalyzed or thermal ynamine-Claisen rearrangement with readily accessible (arylthio)ynamines.*

The Claisen rearrangement has found substantial utility in the methodology of synthetic organic chemistry.[2)] For example, the reaction of an allylic alcohol with ynamines affords the rearranged γ,δ-unsaturated amides via the ketene N,O-acetal intermediates in the so-called ynamine-Claisen rearrangement first developed by Ficini.[3)] More recently Bartlett has reported interesting stereochemical features of the Claisen variant.[4)] We have recently developed an exceedingly convenient method for preparing (arylthio)ynamines (1) from 2,2,2-trifluoroethyl sulfides and secondary amines.[5)] Thus the easy availability of 1, coupled with our continuing interest in synthetic applications of sigmatropic rearrangements,[6)] prompted us to examine the unexplored ynamine-Claisen rearrangement with 1.

Herein we wish to report that the particular ynamine-Claisen rearrangement provides a versatile method for the stereocontrolled synthesis of conjugated dienamides (6). Scheme I illustrates the complete transformation requiring no purification of intermediates. The key step is the facile conversion of an allylic alcohol (2) to the stereochemically defined γ,δ-unsaturated amides (4) which involves addition of 2 to 1 followed by the *in situ* Claisen rearrangement. Oxidation of 4 ($NaIO_4$, aq. CH_3OH) followed by thermolysis of the resulting sulfoxides (5) (reflux in toluene) furnishes (*E*,*E*)-2,4-alkadienamides (6) in good yields (see

Scheme I

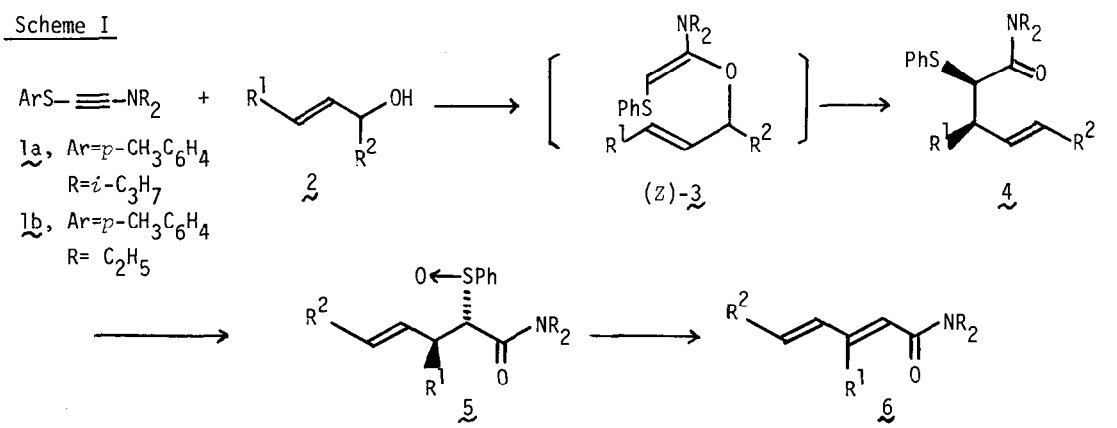
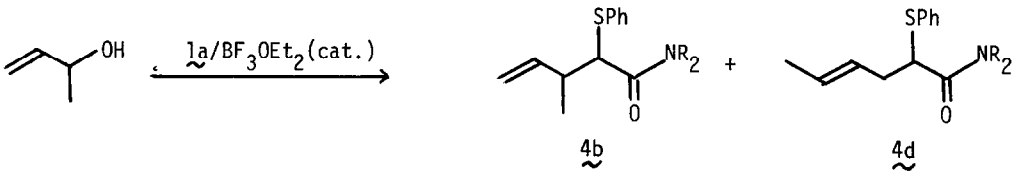


Table 1). The most notable feature of the present method compared with previous ones[7] for 2,4-alkadienoic acid derivatives is that the two olefinic stereochemistries in the product are fully controlled through combination by the ynamine-Claisen rearrangement with thermolysis of the sulfoxides.

The ynamine-Claisen rearrangement was best carried out in ether at 20°C in the presence of boron trifluoride etherate (method A) for primary allylic alcohols (entries 1-4) or in refluxing toluene without any acid catalyst (method B) for secondary allylic alcohols (entries 5-8). Application of method A to secondary allylic alcohols caused a serious regiochemical problem. For instance, the BF_3-catalyzed reaction of 1-buten-3-ol resulted in the formation of a 3 : 4 mixture of amides 4b and 4d arising from the formal [1,3]- and [3,3]-rearrangement, respectively.[8]



4b 4d

The stereochemical features of our synthetic approach are twofold. First, the thermal rearrangement of secondary alcohols 2 (R^1=H, R^2=alkyl) eventually furnishes (2*E*, 4*E*)-alkadienamides with high stereoselectivity. It should be noted that the *E* geometry of the γ,δ-double bond is established by the high stereoselectivity inherent in the Claisen rearrangement[2] whereas the *E* geometry of the α,β-double bond results from the high *E* selectivity[9] generally observed with thermolysis of sulfoxides having two β-hydrogens such as 3 (R^1=H). Secondly, the acid-catalyzed rearrangement of (*E*)-allylic alcohols 2 (R^1=alkyl, R^2=H) is highly diastereoselective, leading selectively to the (2*E*)-dienamides with trisubstituted olefinic bonds.[10] In view of the syn-elimination mechanism widely accepted for the thermal extrusion of sulfenic acid,[9] the geometry of the trisubstituted olefinic bond should be established solely by the relative stereochemisty of the vicinal chiral centers created by the rearrangement. Thus the selective formation of the *E* double bond obviously indicates that the erythro-4b arising from the (*Z*)-ketene N,O-acetal predominates over the threo isomer from the (*E*)-ketene acetal[11] (see Scheme II).

Scheme II

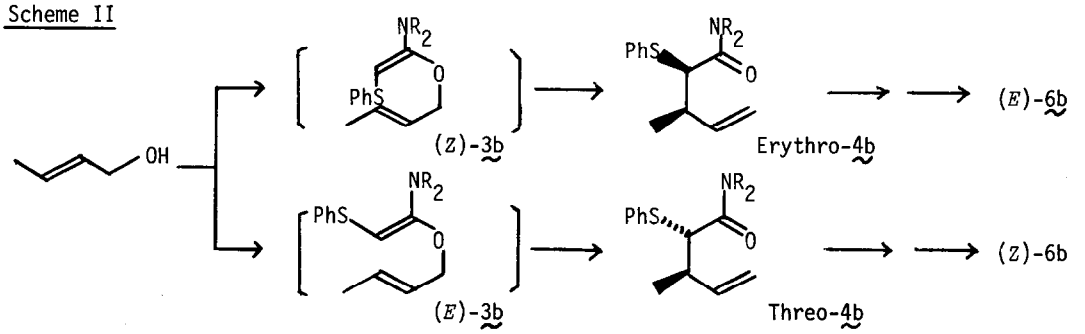
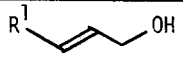
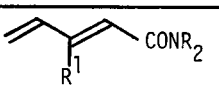
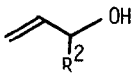
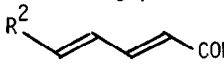
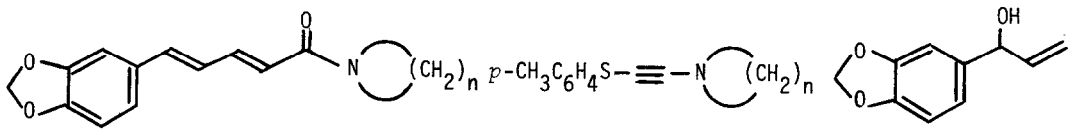


Table 1

Entry	Allylic alcohol	Rearr. method[a] (Ynamine used)	Conjugated dienamide[b]	Overall yield, %[c] (Stereochemistry)[d]
				
1	R^1=H	A (1a)	6a, R^1=H, R=*i*-C_3H_7	81 [*E*, >95%]
2	R^1=CH_3	A (1a)	6b, R^1=CH_3, R=*i*-C_3H_7	72 [*E*, >95%]
3	R^1=CH_3	A[e] (1a)	6b	70 [*E*/*Z*= 3 : 2]
4	R^1=*n*-C_3H_7	A (1a)	6c, R^1=*n*-C_3H_7, R=*i*-C_3H_7	59 [*E*/*Z*= 4 : 1]
				
5	R^2=CH_3	B (1a)	6d, R^2=CH_3, R=*i*-C_3H_7	57 [(2*E*, 4*E*), >95%]
6	R^2=CH_3	B (1b)	6d', R^2=CH_3, R=C_2H_5	67 [(2*E*, 4*E*), >95%]
7	R^2=*n*-C_5H_{11}	B (1a)	6e, R^2=*n*-C_5H_{11}, R=*i*-C_3H_7	56 [(2*E*, 4*E*), >95%]
8	R^2=*n*-C_5H_{11}	B (1b)	6e', R^2=*n*-C_5H_{11}, R=C_2H_5	57 [(2*E*, 4*E*), >95%]

[a] See the text. [b] Fully characterized by spectral (ir and nmr) data. [c] Based on the allylic alcohol (not optimized). [d] Unequivocally determined by nmr analysis (*cf.* ref 10). The nmr data will be described in a full paper. [e] The reaction was run in refluxing ether.

As illustrations of the synthetic utility of the present method, we further carried out the syntheses of naturally occurring dienamides, trichostachine (7)[12] and piperine (8)[13] isolated from *Piper trichostachyon* and *Piper nigrum*, repectively. Thus the thermal rearrangement procedure described above was applied to the reaction of the allylic alcohol (9)[14] with ynamine 1c.[15] Oxidation (*m*-chloroperbenzoic acid, CH_2Cl_2, -78°C)[16] of the rearranged amdie followed by thermolysis afforded 7 in 30% overall yield.[17] Similarly, the use of 1d in place of 1c gave rise to 8 in 30% overall yield.[17] The both alkaloids thus obtained are identical in all respects (mp, ir, and nmr) with the reported ones. Finally, it is interesting to note that (2*E*, 4*E*)-decadienamide (6e) obtained above (entries 7 and 8) is closely related to pellitorine (*N*-isobutyl-2,4-decadienamide), a naturally occurring insecticide isolated from *Anacyclus pyrethrum* roots.[18]



7, n=4; 8, n=5

1c, n=4; 1d, n=5

9

References and Notes

1) A part of this work was presented at the 26th IUPAC Congress, Tokyo, 1977.

2) Reviews: G. B. Bennett, *Synthesis*, 1978, 589; F. E. Ziegler, *Acc. Chem. Res.*, 10, 227 (1977); S. J. Rhoads and N. R. Raulins, *Org. React.*, 22, 1.

3) J. Ficini and C. Barbara, *Tetrahedron Lett.*, 1966, 6425.

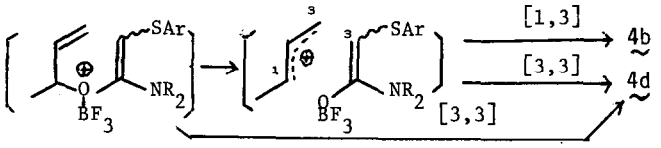
4) P. A. Bartlett and W. F. Hahne, *J. Org. Chem.*, 44, 882 (1979).

5) T. Nakai, K. Tanaka, H. Setoi, and N. Ishikawa, *Bull. Chem. Soc. Jpn.*, 50, 3069 (1977); T. Nakai, K. Tanaka, and N. Ishikawa, *Chem. Lett.*, 1976, 1263.

6) (a) T. Nakai, K. Mikami, S. Taya, Y. Kimura, and T. Mimura, *Tetrahedron Lett.*, 22, 69 (1981);(b) T. Nakai, T. Mimura, and T. Kurokawa, *ibid.*, 1978, 2895, and references cited therein.

7) For leading references, see: ref 6a. For more recent examples, see: K. Tanaka, M. Terauchi, and A. Kaji, *Chem. Lett.*, 1981, 315; Y. Tamura, H.-D. Choi, H. Maeda, and H. Ishibashi, *Tetrahedron Lett.*, 22, 1343 (1981).

8) The undesired amide (4b) could be formed via the dissociation of the ketene N,O-acetal intermediate followed by recombination depicted below.



9) Review: B. M. Trost, *Chem. Rev.*, 78, 363 (1978).

10) The geometry of the trisubstituted double bond was easily determined by nmr spectra. For instance, the γ-hydrogen of (*Z*)-6b is shielded (δ 6.32 (d,d)) relative to that of (*E*)-6b (δ 6.85).

11) The sense and degree of diastereoselection observed with the present Claisen variant is comparable to those recently reported by Bartlett for a different ynamine-Claisen rearrangement with 1-(dimethylamino)propyne (ref 4).

12) For isolation, see: J. Singh, K. L. Dhar, and C. K. Atal, *Tetrahedron Lett.*, 1969, 4975.

13) For isolation and biological activities, see: The Merk Index (9th Ed.), Merk & Co., p.7262.

14) Prepared from piperonal and vinyl Grignard reagent; 71%; bp 121-123°C/3 mmHg.

15) Ynamine 1c and 1d were prepared in 94-98% from *p*-$CH_3C_6H_4SCH_2CF_3$ and pyrrolidine and piperidine, respectively, according to the previously-reported method (ref 5).

16) Periodate oxidation of the amide did not work well because of the low solubility of the amide in aqueous methanol.

17) These low yields seem to arise from the incompleteness of addition of 9 to 1c (or 1d); the addition reaction was quite slow and a part of 9 was polymerized during the reaction.

18) M. Jacobson, "Naturally Occurring Insecticides," M. Jacobson and D. G. Crosby, Ed., Marcel Decker, New York, 1971, p.137.

(Received in Japan 27 June 1981)