Tetrahedron Letters No. 45, pp 4337 - 4340.

0040-4039/78/1101-4337$02.00/0

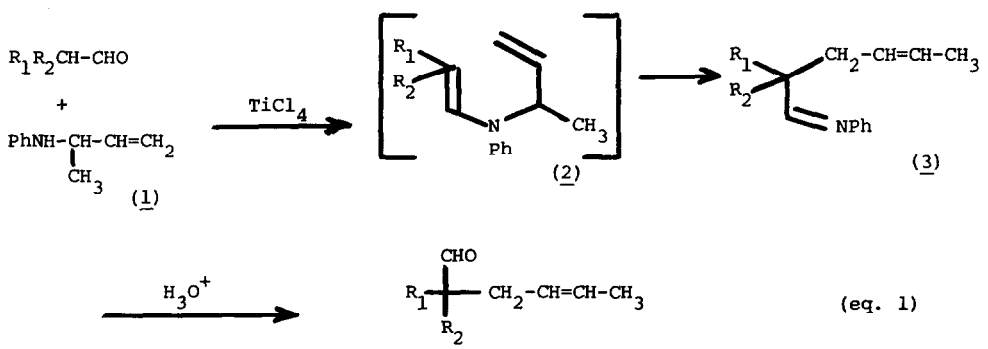
TITANIUM TETRACHLORIDE CATALYSIS OF AZA-CLAISEN REARRANGEMENTS

Richard K. Hill* and Hiralal N. Khatri
Department of Chemistry, University of Georgia, Athens, GA 30602

In attempting to apply the aza-Claisen rearrangement of N-allylenamines[1] to a moderately bulky aldehyde, we encountered difficulty in preparing the enamine with N-phenyl-α-methallylamine (1) by the usual procedures. Since $TiCl_4$ has been reported[2] to catalyze enamine synthesis from hindered carbonyl compounds we were led to try this reagent, and have found that it catalyzes not only enamine formation but sigmatropic rearrangement as well. Although the uncatalyzed aza-Claisen rearrangement[1] requires temperatures near 250°, the presence of 0.25 mole of $TiCl_4$ allows the reaction to occur at a convenient rate in refluxing benzene and at a slow rate even at room temperature.

$TiCl_4$ catalysis of the aza-Claisen rearrangement is consequently another example of "charge-induced" pericyclic reactions[3], a useful and growing reaction type. Lewis acid catalysis of the Claisen rearrangement is well documented[4], and can increase the rate as much as 10^{10}; $TiCl_4$ is among the effective catalysts for the rearrangement of allyl phenyl ethers[5]. Among aza-Claisen rearrangements, $ZnCl_2$ and H_2SO_4 both catalyze the rearrangement of N-allylanilines[6], and it has been known for some time that quaternary salts of N-allylenamines rearrange more rapidly[7] that the parent uncharged amine.

Our discovery of $TiCl_4$ catalysis makes it possible to prepare and rearrange N-allylenamines of aldehydes in a single step, and hydrolytic workup thus provides the alkylated aldehyde in a single operation (eq. 1):



(eq. 1)

The aza-Claisen rearrangement is already a useful alternative to conventional alkylation[1,8], since it requires neither an alkylating agent nor strong base, and this added feature of $TiCl_4$ catalysis should make it even more valuable. A typical experimental procedure follows.

To a solution of 1.3 g (0.01 mole) of 2-phenylpropanal and 1.7 g (0.012 mole) of N-phenyl-α-methallylamine in 30 ml of dry toluene was added 0.31 ml (0.0025 mole) of $TiCl_4$ in 20 ml of dry toluene at -30 to -40° under a nitrogen atmosphere. After the addition, the reaction mixture was allowed to warm to room temperature and then refluxed for 24 hr. The cooled solution was passed through a short florisil column and eluted with ether. The combined eluates were concentrated to give 2.6 g of brown oil, which upon distillation yielded 1.50 g (56.6%) of imine, bp 160-170° (0.6 mm, Kugelrohr). The imine was hydrolyzed by refluxing with 50 ml of 20% hydrochloric acid for 3 hr and the cooled solution was extracted with ether. Workup of the ether extracts gave 0.50 g (47%) of 2-methyl-2-phenyl-4-hexenal (4), bp 150-160° (3 mm).

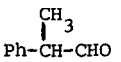
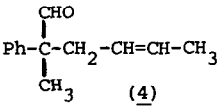
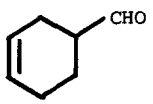
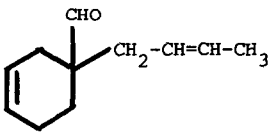
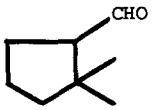
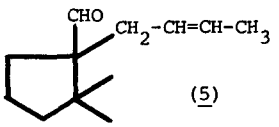
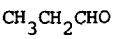
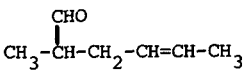
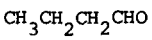
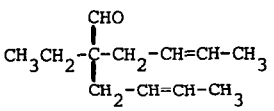
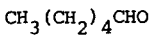
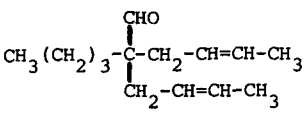
A list of aldehydes studied and their alkylation products is given in Table 1; the readily available[9] allylic amine (1) was used to prepare the enamine in all cases. The first three entries are 2,2-disubstituted aldehydes which smoothly undergo introduction of a C-allyl substituent. Linear aldehydes gave mixed results; although propanal gave the monoalkylated aldehyde, butanal and hexanal both led to products containing two crotyl groups. In these cases the initially formed imine (3) is capable of adding a second mole of amine (1) with subsequent elimination of aniline, to form a second N-allylenamine which can undergo further rearrangement[10]. The catalyzed aza-Claisen rearrangement is thus most suitable for disubstituted aldehyde reactants.

Two simple ketones, acetophenone and cyclohexanone, did not react under comparable conditions. $TiCl_4$ did not catalyze the rearrangement of crotyl vinyl ether.

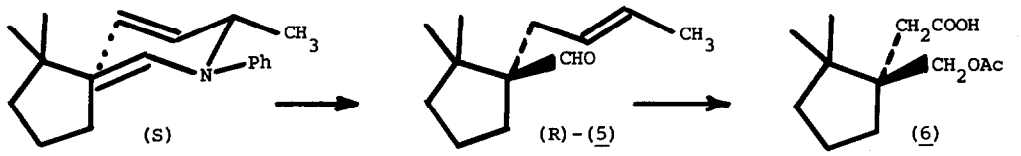
The preformed enamine (2, R_1 = Ph, R_2 = CH_3) from 2-phenylpropanal and amine (1) shows no sign of rearrangement in refluxing toluene for 24 hr, but with the addition of 0.25 mole of $TiCl_4$ rearrangement is complete in 24 hr in refluxing benzene. The catalyzed rearrangement is 68% complete in 24 hr in benzene at 50°, and even at 25° is 67% complete in 72 hr.

Several stereochemical features suggest that $TiCl_4$ does not alter the fundamental mechanism or geometry of the aza-Claisen rearrangement. First, in the case of rearrangement product (4), the ratio of trans to cis double bond isomers is the same within experimental error in the catalyzed and uncatalyzed rearrangements, 90 ± 3 : 10 ± 3. Secondly, when optically active amine (1) is used in the reaction, asymmetric induction takes place in the creation of the new asymmetric center to about the same extent as in the absence of the catalyst. Specifically, when amine of optical rotation $[\alpha]_D^{30}$ + 1.53° ($CHCl_3$), 45.3% e.e., was employed, trans-(4) was isolated with $[\alpha]_D^{30}$ + 8.1°, 15.3% e.e., corresponding to an asymmetric induction of 67%. The non-catalyzed rearrangement is reported[1] to afford trans-(4) with 69% asymmetric induction. Thus it appears that $TiCl_4$ catalysis does not change the characteristic chair-like transition state, with substituents predominantly equatorial, typical of Claisen and other [3,3]-sigmatropic rearrangements.

TABLE 1

Starting Aldehyde	Alkylation Product	Yield
	 (4)	27-68%
		31%
	 (5)	61%
		26%
		16%
		27%

When optically active (S)-(1), $[\alpha]_D^{27}$ -1.47°, was used in the reaction with 2,2-dimethylcyclopentanecarboxaldehyde, the product (5) was isolated after purification by glc as an apparently homogeneous trans aldehyde, $[\alpha]_D^{27}$ -2.53°. Based on the favored transition state conformation this aldehyde can be predicted to have the (R) configuration:



(S) (R)-(5) (6)

Compound (5) has been converted by $NaBH_4$ reduction, acetylation, and permanganate oxidation to (6), an attractive intermediate for the synthesis of optically active polyzonimine[11], a millipede pheromone, further illustrating the potential of the catalyzed aza-Claisen rearrangement for the construction of chiral centers in predictable configuration.

REFERENCES

1. R.K. Hill and N.W. Gilman, Tetrahedron Lett., 1421 (1967).
2. W.A. White and H. Weingarten, J. Org. Chem., 32, 213 (1967).
3. For a survey of this reaction type, see U. Widmer, J. Zsindely, H.-J. Hansen, and H. Schmid, Helv. Chim. Acta, 56, 75 (1973).
4. See, e.g., J. Borgulya, R. Madeja, P. Fahrni, H.-J. Hansen, H. Schmid, and R. Barner, Helv. Chim. Acta, 56, 14 (1973).
5. K. Narasaka, E. Bald, and T. Mukaiyama, Chem. Lett. (Tokyo), 1041 (1975).
6. (a) M. Schmid, H.-J. Hansen, and H. Schmid, Helv. Chim. Acta, 56, 105 (1973); (b) S. Jolidon and H.-J. Hansen, ibid., 60, 978 (1977).
7. (a) K.C. Brannock and R.D. Burpitt, J. Org. Chem., 26, 3576 (1961); (b) G. Opitz, Justus Liebig's Ann. Chem., 650, 122 (1961).
8. (a) R.K. Hill and G.R. Newkome, Tetrahedron Lett., 5059 (1968); (b) P.M. McCurry, Jr. and R.K. Singh, ibid., 3325 (1973).
9. M.E. Synerholm, N.W. Gilman, J.W. Morgan, and R.K. Hill, J. Org. Chem., 33, 1111 (1968).
10. Cf. the dialkylation of enamines with allyl halides: M.E. Kuehne, in Enamines: Synthesis, Structure and Reactions (A.G. Cook, ed.), Marcel Dekker, New York, 1969, p. 352.
11. J. Smolanoff, A.F. Kluge, J. Meinwald, A. McPhail, R.W. Miller, K. Hicks, and T. Eisner, Science, 188, 734 (1975).

(Received in USA 11 August 1978)