REACTIONS OF N-PHENYL-β-AMINOALCOHOLS WITH ACETYLENIC ESTERS

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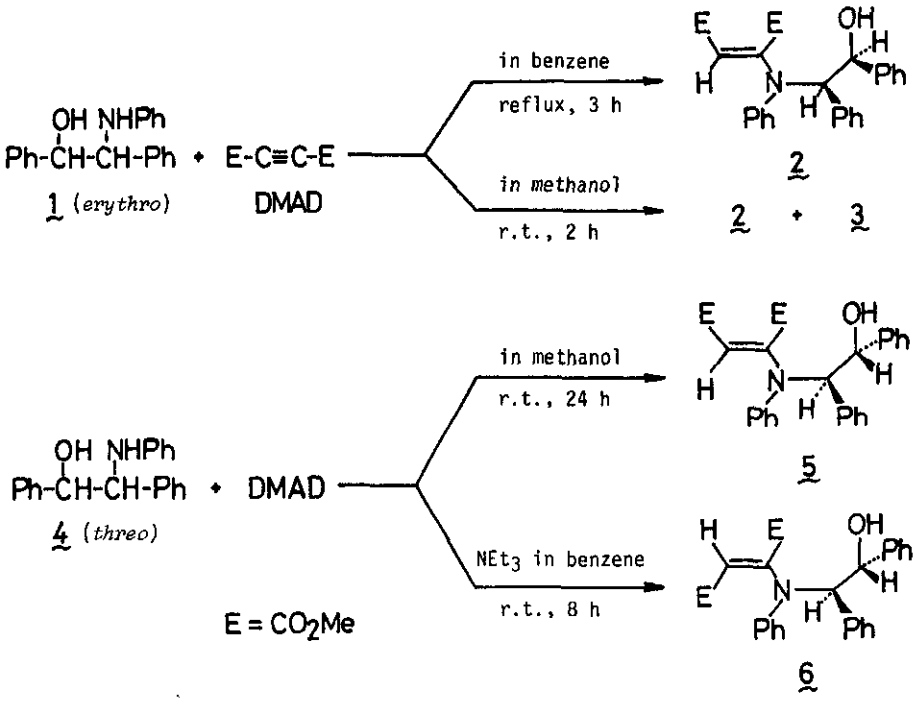
Abstract —— *erythro*-1,2-Diphenyl-2-phenylaminoethanol 1 reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing benzene to give the *cis*-Michael adduct, whereas the same reaction in methanol at room temperature afforded a mixture of the Michael adduct and tetrahydro-1,4-oxazepin-7-one derivative. Although *threo*-isomer 4 was less reactive than 1, 4 reacted with DMAD in methanol or in the presence of triethylamine in benzene at room temperature to give the *cis*- or *trans*-Michael adduct, respectively. Photochemical and acid-catalyzed transformations of the Michael adducts to 1,4-oxazepine and oxazolidine derivatives are also described. The reaction of *cis*-1-hydroxy-2-phenylaminoacenaphthene 10 with DMAD gave the *trans*-Michael adduct, which on heating in acetic acid was converted into the corresponding oxazolidine. On the other hand, 1, 4, and 10 reacted with methyl phenylpropiolate in the presence of triethylamine in refluxing xylene afforded the corresponding oxazolidin-2-ones.

It has been reported that N-unsubstituted β-aminoalcohols reacted with acetylenic esters to give the corresponding 1,4-oxazinones with the elimination of an alcohol[1,2]. A 1,4-oxazinone was used for the preparation of an optically active amino acid[2]. Few reactions of N-substituted β-aminoalcohols with acetylenic esters, however, have so far been reported. In the present communication we wish to report the reactions of N-phenyl-β-aminoalcohols with dimethyl acetylenedicarboxylate (DMAD) and methyl phenylpropiolate, resulting in the reaction patterns quite different from those of N-unsubstituted β-aminoalcohols.

The reaction of *erythro*-1,2-diphenyl-2-phenylaminoethanol 1[3] with two equimolar amounts of DMAD in refluxing benzene did not give the expected 1,4-oxazinone, but instead a Michael adduct 2 was obtained in 75% yield as the sole product. In the reaction in methanol at room temperature, however, 1 afforded 2 and a new product 3 in 25 and 38% yields, respectively. Although *threo*-1,2-diphenyl-

2-phenylaminoethanol 4[3] did not react with DMAD even in refluxing xylene, the same reaction in methanol or in the presence of triethylamine[4] in benzene at room temperature afforded a Michael adduct 5 or its stereo isomer 6 in 49 or 33% yield respectively (Scheme 1).



Scheme 1

Structural elucidation of the Michael adducts 2, 5, and 6 was accomplished on the basis of spectral data[5]. It is known that, in the nmr spectra of Michael adducts derived from alcohols[4] or secondary amines[6] and DMAD, the olefinic protons of *trans*-adducts appear at lower field than those of corresponding *cis*-adducts. Thus it can be concluded that 5 showing the olefinic proton at δ 4.43 is *cis*-adduct, whereas 6 showing it at δ 5.03 is *trans* one. It is also deduced that 2 is *cis*-adduct since the chemical shift of olefinic proton in 2 is comparable to that in 5. The structure of 3 will be described later.

The molecular formula of 3 corresponds to that of compound derived from a 1:1 adduct with the elimination of methanol. However, 2 was unchanged even in refluxing methanol, indicating that 3 was arisen from a 1:1 adduct other than 2. On the basis of the following experiment, it was deduced that 3 was derived from the *trans* isomer of 2.

Irradiation of a solution of 2 in benzene with Pyrex-filtered light from a 300-W high-pressure mercury lamp (Taika HLV-8) under nitrogen afforded 3 and a new compound 7 whose molecular formula corresponds to that of a 1:1 adduct. Irradiation of 2 in other solvents afforded 3 as the sole isolated product[7]. The results are given in Table I.

Table I. Photochemical Reaction of 2

Solvent	Irradiation time, min	Product, % 3	7
benzene	10	32	14
benzene	30	49	14
ethyl ether	30	45	—
methanol	30	51	—
ethanol	30	40	—

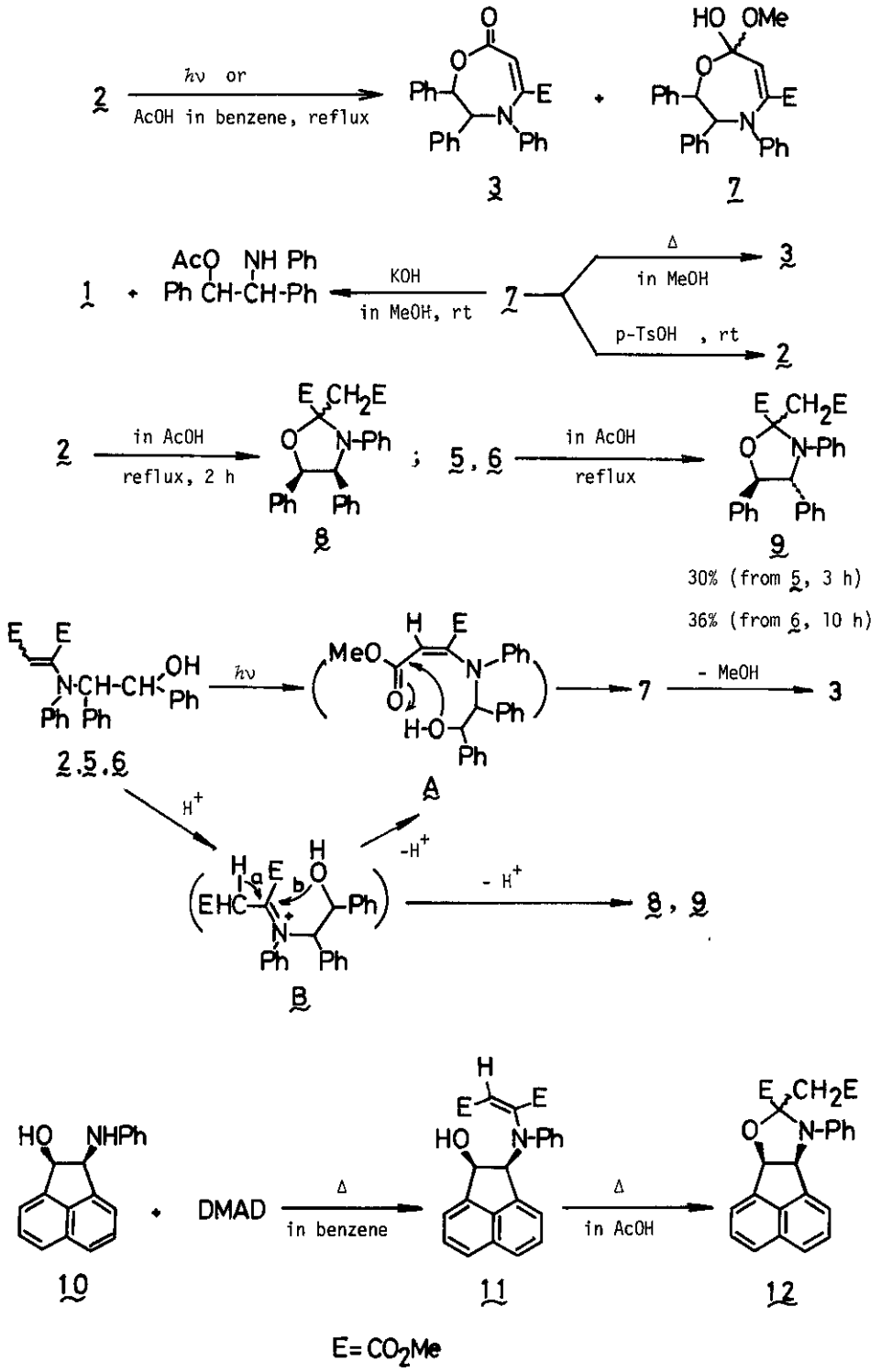
When treated with a catalytic amount of acetic acid in refluxing benzene for 2 h, 2 gave 3 and 7 in 16 and 42% yields respectively. In a similar treatment, however, both 5 and 6 were unchanged. The compound 7 was readily transformed into 3 on heating in methanol under reflux, indicating that 7 is a precursor for 3. Treatment of 7 with p-toluenesulfonic acid in ethyl ether at room temperature gave 2 in a quantitative yield, while 7 was treated with methanolic potassium hydroxide at room temperature to give a mixture of 1 (15%) and its O-acetyl derivative (39%), mp 102-103°C.

On the basis of the above observations as well as spectral data[8], 3 was deduced as 2,3,4,7-tetrahydro-5-methoxycarbonyl-2,3,4-triphenyl-1,4-oxazepin-7-one, and 7 as its hemiacetal.

In contrast to the above results, 2 was converted into *cis*-4,5-diphenyloxazolidine 8 on heating in acetic acid. Similarly, 5 and 6 were converted into the same *trans*-4,5-diphenyloxazolidine 9 (Scheme 2). Structural elucidation of 8 and 9 was accomplished on the basis of spectral data[9].

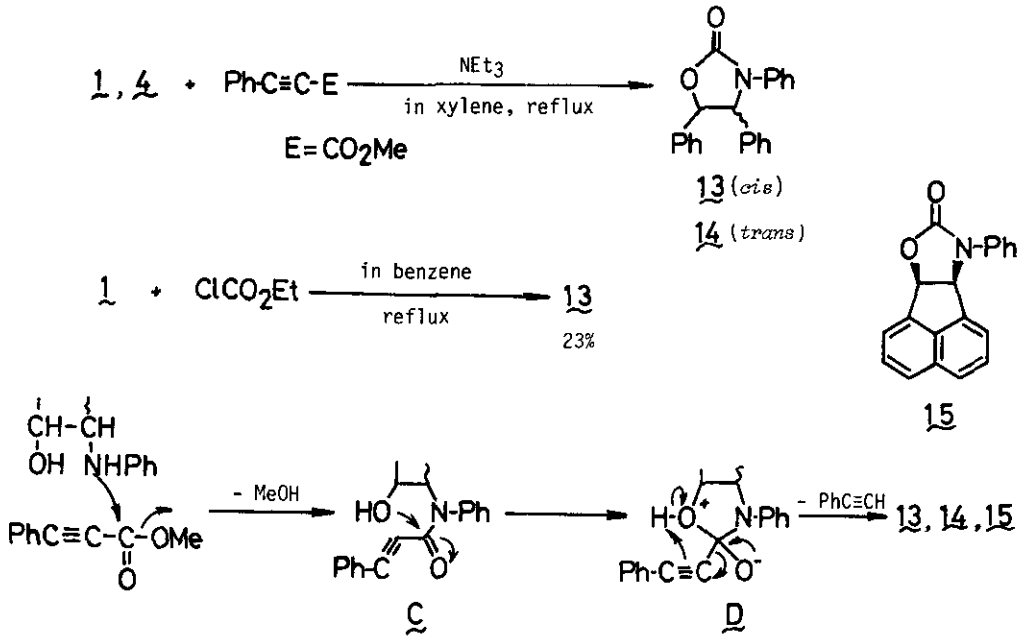
The pathways for the formation of 3, 7, 8, and 9 can be illustrated as shown in Scheme 2. Upon irradiation 2 isomerizes to *trans*-adduct A, which cyclizes to 1,4-oxazepinone hemiacetal 7. Subsequent elimination of methanol from 7 gives stable oxazepinone 3. On the other hand, protonation takes place at the β-carbon atom to yield B, since the Michael adducts 2, 5, and 6 have an enamine structure. When a catalytic amount of acetic acid is present, B generated from 2 partially undergoes an isomerization to A (path a) and a cyclization to oxazolidine 8 (path b) with concurrent deprotonation, whereas B generated from 5 or 6 reverts to the original Michael adduct respectively. In refluxing acetic acid, however, B generated from 2, 5 or 6 is transformed into 8 or 9 via the path b.

The reaction of *cis*-1-hydroxy-2-phenylaminoacenaphthene 10[10] with DMAD in refluxing benzene for 6 h afforded a 72% yield of *trans*-Michael adduct 11, which on heating in acetic acid for 4 h was converted into oxazolidine derivative 12 in 80% yield. The structures of 11 and 12 were again confirmed on the basis of spectral data[11].


hν or
AcOH in benzene, reflux
KOH
in MeOH, rt
Δ
in MeOH
p-TsOH , rt
in AcOH
reflux, 2 h
in AcOH
reflux
30% (from 5, 3 h)
36% (from 6, 10 h)
hν
- MeOH
H+
-H+
- H+
DMAD
Δ
in benzene
Δ
in AcOH
E= CO2Me

Scheme 2

Next, we have investigated the reaction of 1, 4 and 10 with methyl phenylpropiolate (MPP). The reaction of 1 with MPP in the presence of triethylamine[12] in refluxing xylene for 4 h afforded *cis*-3,4,5-triphenyloxazolidin-2-one 13, which was identical with the authentic sample prepared from 1 and ethyl chloroformate, in 56% yield. Under similar conditions for 10 h, 4 and 10 reacted with MPP to give the corresponding oxazolidinones 14 and 15 in 29 and 43% yields, respectively[13].



Scheme 3

The pathway for the formation of oxazolidinones can be explained as shown in Scheme 3. The reaction proceeds via an initial nucleophilic attack of the amino group on the carbonyl carbon atom in MPP, followed by elimination of methanol to yield C. Subsequent elimination of phenylacetylene from cyclic intermediate D which generated from C gives oxazolidinones.

REFERENCES AND NOTES

1. Y. Iwanami, Nippon Kagaku Zasshi, 1961, 82, 780.
2. J. P. Vigneron, H. Kagan, and A.Horeau, Tetrahedron Lett., 1968, 5681.
3. The compounds 1, mp 119-120°C (lit.[14] mp 119°C) and 4, mp 112-113°C (lit.[15] mp 112°C) were prepared by the reported methods, respectively.
4. It has been reported that tertiary amines catalyze the reaction of alcohols with DMAD (E. Winterfeldt and H. Preuss, Chem. Ber., 1966, 99, 450).
5. All new compounds in this paper gave satisfactory elemental analyses. 2: mp 134-136°C; colorless prisms; ir (KBr) 3550, 1730, 1690 cm^{-1}; nmr ($CDCl_3$) δ 2.06 (1H, broad, OH), 3.53, 3.60 (each 3H, s), 4.62 (1H, s, =CH), 5.16, 5.35 (each 1H, d, ≥CH, J=7.0 Hz), 6.75-7.93 (15H, m);

MS m/e 431 (M^+). 5: mp 172-174°C; colorless prisms; ir (KBr) 3460, 1750, 1670 cm^{-1}; nmr ($CDCl_3$) δ 3.40 (1H, broad, OH), 3.59, 4.13 (each 3H, s), 4.43 (1H, s, =CH), 5.00, 5.06 (each 1H, pseudo d, ≥CH), 6.70-7.80 (15H, m); MS m/e 431 (M^+). 6: mp 128-130°C; colorless prisms; ir (KBr) 3530, 1750, 1700 cm^{-1}; nmr ($CDCl_3$) δ 3.59, 3.89 (each 3H, s), 4.55-4.80 (1H, broad, OH), 4.65, 5.13 (each 1H, pseudo d, ≥CH), 5.03 (1H, s, =CH), 6.47-8.05 (15H, m); MS m/e 431 (M^+).

6. J. E. Doffini, J. Org. Chem., 1965, 30, 1298.
7. Irradiation of 5 and 6 under similar conditions afforded no identified products.
8. 3: mp 234°C; yellow prisms; ir (KBr) 1750, 1700 cm^{-1}; nmr ($CDCl_3$) δ 3.27 (3H, s), 5.22, 6.09 (each 1H, d, ≥CH, J=3.0 Hz), 6.15 (1H, s, =CH), 6.66-7.80 (15H, m); MS m/e 399 (M^+). 7: mp 147-149°C (dec); yellow prisms; ir (KBr) 3410, 1720 cm^{-1}; nmr (benzene-d_6) δ 3.13, 3.25 (each 3H, s), 4.30 (1H, broad, OH), 5.51, 5.61 (each 1H, d, ≥CH, J=3.0 Hz), 6.69 (1H, s, =CH), 6.60-7.60 (15H, m).
9. 8: mp 115-116°C; colorless prisms; ir (KBr) 1735 cm^{-1}; nmr ($CDCl_3$) δ 3.72, 3.76 (each 3H, s), 3.39, 3.85 (each 1H, d, J=15.0 Hz), 5.34, 6.04 (each 1H, d, ≥CH, J=8.0 Hz), 6.65-7.40 (15H, m); MS m/e 431 (M^+). 9: mp 104-105°C; colorless prisms; ir (KBr) 1740 cm^{-1}; nmr ($CDCl_3$) δ 3.60 (2H, s), 3.57, 4.00 (each 3H, s), 4.92, 5.29 (each 1H, d, ≥CH, J=9.0 Hz), 6.60-7.57 (15H, m); MS m/e 431 (M^+).
10. O. Tsuge, M. Tashiro, and K. Oe, The Report of Research Institute of Industrial Science, Kyushu University, 1970, No. 51, 7.
11. 11: mp 146-148°C; colorless prisms; ir (KBr) 3580, 1730, 1690 cm^{-1}; nmr (pyridine-d_5) δ 3.57, 3.82 (each 3H, s), 5.35 (1H, s, =CH), 6.03, 6.17 (each 1H, d, ≥CH, J=7.0 Hz), 6.60-8.05 (12H, m, ArH + OH); MS m/e 403 (M^+). 12: mp 175-177°C; colorless prisms; ir (KBr) 1730 cm^{-1}; nmr ($CDCl_3$) δ 2.82, 3.72 (each 3H, s), 3.03, 3.28 (each 1H, d, J=15.0 Hz), 5.89, 6.37 (each 1H, d, ≥CH, J=8.0 Hz), 6.90-8.05 (11H, m); MS m/e 403 (M^+).
12. The reaction without triethylamine did not occur.
13. 13: mp 223-224°C; colorless prisms; ir (KBr) 1760 cm^{-1}; nmr ($CDCl_3$) δ 5.55, 6.01 (each 1H, d, ≥CH, J=8.0 Hz), 6.80-7.70 (15H, m); MS m/e 315 (M^+). 14: mp 110-112°C; colorless prisms; ir (KBr) 1760 cm^{-1}; nmr ($CDCl_3$) δ 5.19, 5.34 (each 1H, d, ≥CH, J=8.0 Hz), 7.04-7.80 (15H, m); MS m/e 315 (M^+). 15: mp 252-253°C; colorless prisms; ir (KBr) 1740 cm^{-1}; nmr ($CDCl_3$) δ 6.23, 6.40 (each 1H, d, ≥CH, J=8.0 Hz), 7.10-8.05 (11H, m); MS m/e 287 (M^+).
14. K. Voigt, J. prak. Chem., 1886, 34, 9.
15. G. Hesse, H. Wilte, and W. Gulden, Angew. Chem., 1965, 77, 591.

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