A NOVEL ROUTE TO 1-AZAAZULENES BY THE REACTION OF β-AMINO ENONES WITH ACTIVATED TROPONES[1]

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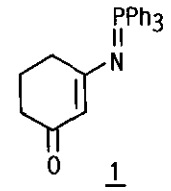
Abstract---The reaction of β-amino enones with activated tropones (2-bromo-, 2-chloro-, and 2-tosyloxytropones) underwent an enamine alkylation followed by dehydrating condensation to give 1-azaazulene derivatives in modest yields.

Previously, we have accomplished a simple preparation of (vinylimino)phosphoranes, which reacted with α-bromo ketones, α,β-unsaturated ketones, tropones and their vinylogues in an enamine alkylation process followed by an aza-Wittig reaction to provide novel routes to pyrroles,[2] pyridines,[3] 1-azaazulenes,[4] and their vinylogues.[5] Although the (vinylimono)phosphorane is considered to be an equivalent of enamine, like enols, enamines are generally unstable and undergo a rapid conversion into the imine tautomer. Thus, simple enamines are inconvenient for the construction of nitrogen heterocycles. However, β-amino enones are widely available and used for the synthesis of pyridines[6] and pyrroles.[7] For recent example, 3-amino-2-cyclohexen-1-one (2a), which is an equivalent of [(3-oxo-1-cyclohexenyl)imino]triphenylphosphorane (1),[8] has been used for the synthesis of 1,5,6,7-tetrahydro-4H-indol-4-ones and 7,8-dihydro-5(8H)-quinolines.[9-13] The homo-



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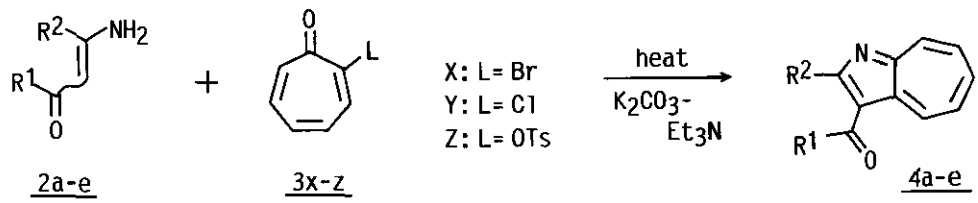


Scheme 1 a: R^1-R^2 = -$(CH_2)_3$- ; b: R^1-R^2 = -$CH_2CMe_2CH_2$-
c: R^1-R^2 = -$(CH_2)_4$- ; d: R^1 = R^2 = Me ; e: R^1 = OMe , R^2 = Me

logue, 3-amino-2-cyclohepten-1-one (2c), reacted also with propenal to give 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine-5-one.[14] On the other hand, 1-morpholinocyclohexene, 1-morpholinocycloheptene, and 1-morpholinopropene reacted with tropone[15] and 2-chlorotropone[16] to give 1,8-cycloadduct or 1,4-cycloadduct. In connection with a series of studies on (vinylimino)phosphoranes, we studied here on the novel reaction of β-amino enones (2a-e) with 2-substituted tropones (3x-z) to give 1-azaazulene derivatives (4a-e) (Scheme 1). The results are described in this paper.

General procedure for the reactions was as follows. A solution of 2[14,17] (1 mmol), 2-substituted tropone (3) (1 mmol or 0.5 mmol), triethylamine (3 mmol), and pottasium carbonate (3 mmol) in anhydrous dioxane (5 ml) was heated under reflux in nitrogen atmosphere untill almost all 3 disappeared. The separation of the products was performed through tlc on silica gel (hexane-AcOEt: 9/1). The reaction conditions and the yields of the products are summarized in Table 1.

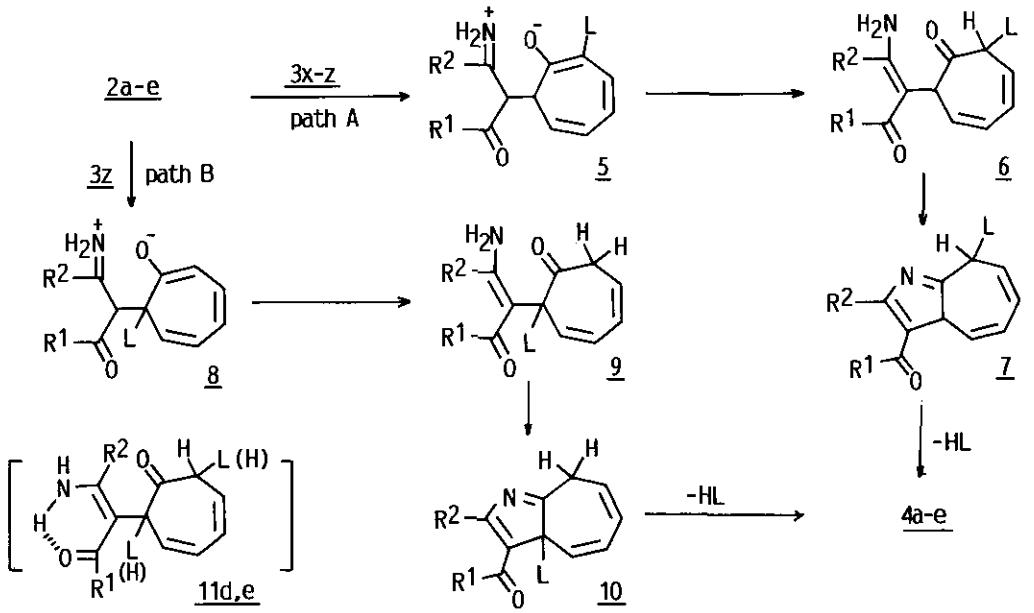
The reaction of 2a,b with 3x-z afforded 1,2,3,4-tetrahydrocyclohepta[b]indol-1-one (4a) (entries 1-3) and its 3,3-dimethyl analogue (4b) (entries 4-6), respectively. The reaction of 2b with 3z in benzene required prolonged heating and resulted in a slight lower yield of 4b (entry 7). Similarly, 2c with 3x,z gave 2,3,4,5-tetrahydro-1H-dicycloheptapyrrole-1-one (4c) (entries 8 and 9). The acyclic β-amino enone (2d,e) with 3x,z proceeded similarly and resulted in poor yields of 2,3-disubstituted cyclohepta[b]pyrroles (4d,e) (entries 10-13). The structures of 4a-e were confirmed on the basis of the physical data (Table 2) as well as comparison of their spectral data with those reported in the literatures.[4,18]

The present reactions are best explained by the mechanistic pathways shown in Scheme 2. Nucleophilic substitution onto a tropone nucleus carrying a mobile substituent is known to take place at C-2 (normal substitution) and/or C-7 (abnormal substitution) to give 2-substituted tropones.[19] Thus, the enamine alkylation process of 2 onto 3x-z gives the intermediate (5), hydrogen migration of which generates a new enamine (6) (Path A). The intramolecular condensation and subsequent elimination of HL results in the formation of 4. The pathway similar to this process was confirmed previously by using 2-bromo-3,5,7-trideuteriotropone and [(1-phenylvinyl)imino]phosphorane.[4] Furthermore, the reaction of 2 with 3z would also follow path B in addition to Path A.[19] The Path B involves an enamine alkylation onto C-7 of 3z to give 8, hydrogen migration of which gives 9. The dehydrating condensation and subsequent elimination of HL gives 4.

Table 1. Reaction of β-Amino Enones (2a-e) with 2-Substituted Tropones (3x-z)

Entry	2	3	Ratio of 3/2	Solvent[a)]	Reaction time/h	Product	Yield/%[b)]
1	2a	3x	0.5	Dioxane	6	4a	50
2	2a	3y	1.0	Dioxane	8.5	4a	51
3	2a	3z	1.0	Dioxane	4	4a	56
4	2b	3x	0.5	Dioxane	6	4b	46
5	2b	3y	1.0	Dioxane	8.5	4b	51
6	2b	3z	1.0	Dioxane	2.5	4b	49
7	2b	3z	1.0	C_6H_6	10	4b	46
8	2c	3x	1.0	Dioxane	7	4c	41
9	2c	3z	1.0	Dioxane	4	4c	26
10	2d	3x	0.5	Dioxane	24	4d	15
11	2d	3z	1.0	Dioxane	8.5	4d	17
12	2e	3x	0.5	Dioxane	19	4e	19
13	2e	3z	1.0	Dioxane	9	4e	24

a) 3 Molar equivalents of K_2CO_3 and NEt_3 were added. b) Yields are based on the compounds (3) used.



Scheme 2

Table 2. Physical Data of 1-Azaazulene Derivatives (4a-e)

4a: oil; ir ($CHCl_3$), 1646 cm^{-1}; ^1H-nmr (90 MHz, $CDCl_3$), δ : 2.13-2.57 (2H, m, H-b), 2.71 (2H, t, J=6.1 Hz, H-4), 3.29 (2H, t, J=6.1 Hz, H-2), 7.80-8.13 (3H, m, H-6, 7, and 8), 8.90-8.86 (1H, m, H-5), 9.13-9.73 (1H, m, H-9). Found: m/z 197.0814. Calcd for $C_{13}H_{11}NO$: 197.0841.

4b: (picrate mp 190-192 C); ir ($CHCl_3$), 1642 cm_{-1}; ^1H-nmr (90 MHz, $CDCl_3$), δ : 1.19 (6H, s, Me-3), 2.59 (2H, s, H-4), 3.19 (2H, s, H-2), 7.83-8.09 (3H, m, H-6, 7, and 8), 8.58-8.82 (1H, m, H-5), 9.43-9.68 (1H, m, H-9). Found: m/z 225.1171. Calcd for $C_{15}H_{15}NO$: 225.1154.

4c: oil; ir ($CHCl_3$), 1628 cm^{-1}; ^1H-nmr (90 MHz, $CDCl_3$), δ : 1.56-2.13 (4H, m, H-3 and 4), 2.88 (2H, t, J=6.0 Hz, H-5), 3.45 (2H, t, J=6.0 Hz, H-2), 7.50-8.03 (3H, m, H-7, 8, and 9), 8.26-8.70 (1H, m, H-6), 9.20-9.63 (1H, m, H-10). Found: m/z 211.0997. Calcd for $C_{14}H_{13}NO$ 211.0997.

4d: oil; ir ($CHCl_3$), 1691 cm^{-1}; ^1H-nmr (90 MHz, $CDCl_3$), δ : 2.72 (3H, s, Me-2), 3.04(3H, s, Me-3), 7.71-8.02 (3H, m, H-5, 6, and 7), 8.46-8.73 (1H, m, H-8), 9.40-9.67 (1H, m, H-4). Found: m/z 185.0852. Calcd for $C_{12}H_{11}NO$ 185.0841.

4e: oil; ir ($CHCl_3$), 1691 cm^{-1}), ^1H-nmr (90 MHz), $CDCl_3$), δ : 3.01 (3H, s, Me-2), 4.00 (3H, s, Me-3), 7.73-8.06 (3H, s, H-5, 6, and 7), 8.50-8.73 (1H, m, H-8), 9.30-9.76 (1H, m, H-4). Found: m/z 201.0768. Calcd for $C_{12}H_{11}NO_2$ 201.0790.

The better yields were obtained for 4a-c as compared to those for 4d,e. Regarding the intermediates (6) and (9), the geometry, in which the amino group is fixed syn to the cycloheptadienone moiety, is favorable for dehydrating condensation giving 7 and 10. This geometry is the only possibility for the cases of cyclic β-amino enones (2a-c). On the other hand, acyclic β-amino enones (2d,e) would also have a possibility to give intermediates (11d,e), in which the amino group is located anti to the cycloheptadienone moiety, because of a stabilizing effect by hydrogen bonding.[20] Although the geometry in 11d,e is unfavorable for dehydrating condensation, an equilibrium between 11d,e and 6d,e (or 9d,e), which collapse to 7d,e (or 10d,e), would be possible. However, the details for poor yield of 4d,e are still unclear here.

Attempted reaction of electron deficient (vinylimino)phosphorane[8] (1) with bromotropone (3x) did not proceed and the starting materials were recovered. Thus, the

present reaction could serve as a convenient route to 1-azaazulenes annulated with cycloalkanones.

ACKNOWLEDGEMENT

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REFERENCES

1. Part 18 of the reaction of (vinylimino)phosphoranes and related compounds. Part 17: M. Nitta, H. Soeda, S. Koyama, and Y. Iino. Bull. Chem. Soc. Jpn., in submission.
2. Y. Iino, T. Kobayashi, and M. Nitta, Heterocycles, 1986, 24, 2437; T. Kobayashi, Y. Iino, and M. Nitta, Nippon Kagaku Kaishi, 1987, 1237.
3. T. Kobayashi and M. Nitta, Chem. Lett., 1986, 1549; Y. Iino and M. Nitta, Bull. Chem. Soc. Jpn., 1988, 61, 2235; N. Kanomata and M. Nitta, J. Chem. Soc., Perkin Trans. 1, 1990, 1119; M. Nitta and Y. Iino, J. Chem. Soc., Perkin Trans.1, 1990, 435.
4. M. Nitta, Y. Iino, E. Hara, and T. Kobayashi, J. Chem. Soc., Perkin Trans. 1, 1989, 51.
5. N. Kanomata and M. Nitta, Tetrahedron Lett., 1990, 31, 1291.
6. G. Jones, "Complehensive Heterocyclic Chemistry," ed. by A. J. Boulton and A. Mckillop, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, and Frankfurt, 1984, Vol. 2, pp. 457-460.
7. R. J. Sundberg, "Complehensive Heterocyclic Chemistry," ed. by C. W. Bird and G. W. H. Cheeseman, Pergamon Press, Oxford, New York, Toronto, Sydney, Paris, and Frankfurt, 1984, Vol. 4, pp. 331-334.
8. M. Nitta, H. Soeda, and Y. Iino, Bull. Chem. Soc. Jpn., 1990, 63, 932.
9. P. G. Baraldi, D. Simoni, and S. Manfredini, Synthesis, 1983, 902.
10. F. Yuste and R. Sanchez-Obregon, J. Org. Chem., 1982, 47, 3665.
11. E. Reimann and J. M. Friesinger, Arch. Pharm. (Weinheim, Ger.), 1985, 318, 871.
12. L. Rondahl, Acta Pharm. Suec., 1980, 17, 288.
13. S. Tori, T. Inokuchi, and M. Kubota, Synthesis, 1986, 400.
14. W. Dammertz and E. Reimann, Arch. Pharm., 1977, 172.
15. M. Oda, M. Funamizu, and Y. Kitahara, Chem. Commun., 1969, 737.
16. M. Oda and Y. Kitahara, Synthesis, 1971, 368.

17. M. J. Lacey, Aust. J. Chem., 1970, 23, 841; P. G. Baraldi, D. Simoni, and S. Manfredini, Synthesis, 1983, 902.

18. Y. Iino, H. Hara, and M. Nitta, Bull. Chem. Soc. Jpn., 1989, 62. 1913.

19. G. Biggi, F. Del Cima, and F. Pietra, J. Am. Chem. Soc., 1973, 95, 7101; F. Pietra, J. Chem. Soc., Chem. Commun., 1974, 444; and references cited therein.

20. T. Tokumitsu and T. Hayashi, Nippon Kagaku Kaishi, 1973, 2152.

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