Notes

Mobile Keto Allyl Systems. 18.[1a] Synthesis and Chemistry of N-Substituted and N,N-Disubstituted 2-Benzoyl-1-amino-3-propenes[1b]

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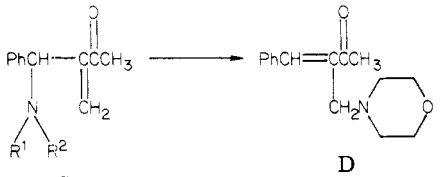
Introduction

Primary allyl halides have been found to react with primary and secondary amines to yield mainly normal substitution products.[2] However, certain functionalized primary allyl halides have been found in this laboratory to produce rearrangement–substitution products. Kinetic studies[1,3] have shown these to be overall second-order reactions which we have described as S_N2' processes.

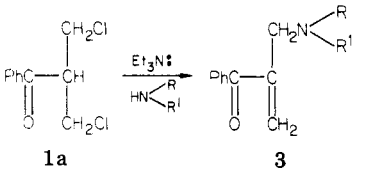
Amino ketones such as B (Scheme I) have been important to us in the synthesis of azetidinyl ketones[4] C. Compound B, where $NR_1R_2 = C_4H_9NH$, reacted with morpholine to yield D, with no 1,3-diamino compound being formed.[1] Thus, amine exchange, in such systems,



B D

is consistent with an S_N2' mechanism where the β-carbonyl function supports a major portion of the developing negative charge in a dipolar transition state.[5]

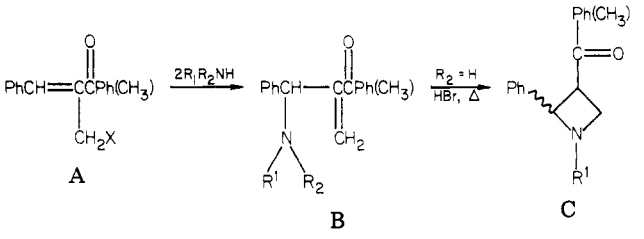
Piskov[6] first prepared compounds of type **3** (R, R^1 = alkyl) in an effort to form compounds analogous to 3-[(diethylamino)methyl]-3-buten-2-one which has been claimed to exhibit marked antiblastic action.



1a 3

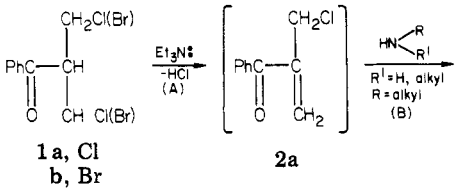
The results of our investigations have clearly indicated that there is a significant difference in the behavior of β-keto allyl halides with amines when a phenyl group is not present on the γ-carbon atom of the allyl system. (For a discussion of the chemistry of related allyl systems see ref 1, 3, and 5.)

Scheme I

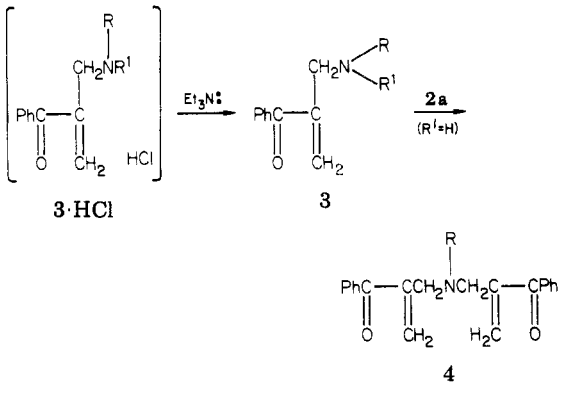


A B C

Scheme II

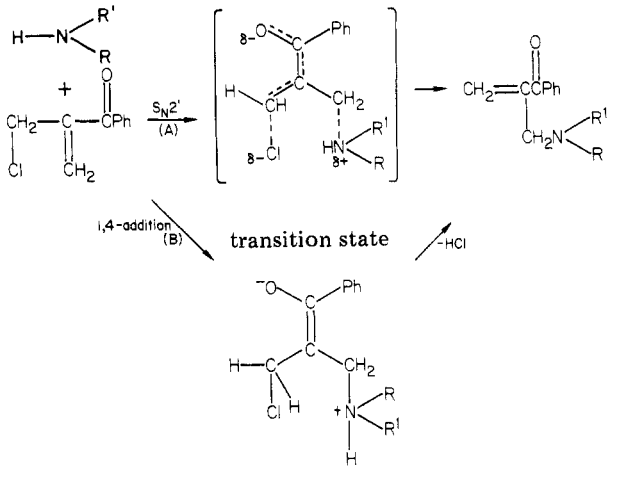


1a, Cl b, Br 2a



3·HCl 3 4

Scheme III



(dipolar intermediate)

Results and Discussion

We have found that the reaction of **1** with amines occurs in at least two steps (Scheme II): (A) elimination of HCl to form **2a** which (B) is subsequently attacked by the appropriate primary or secondary amine to yield **3**; see

(1) (a) For Paper 17 in this series, see: Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 3863. (b) Presented in part before the Second Chemical Congress of the North American Continent, San Francisco, CA, Aug 29, 1980, NO-ORGN359.

(2) (a) Bordwell, F. G.; and Schemayder, D. A. *J. Org. Chem.* **1968**, *33*, 3240. (b) Valkanas, G.; Waight, E. S. *J. Chem. Soc.* **1964**, 531. (c) DeWolfe, R. H.; Young, W. G. "The Chemistry of Alkenes"; Patai, S., Ed.; Wiley: New York, 1964; Vol. 1, p 681.

(3) George, A. D.; Doomes, E.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3918.

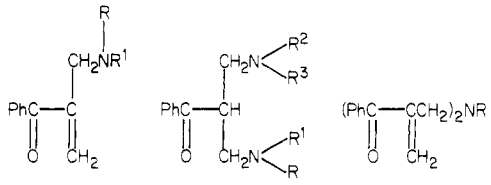
(4) Eagen, M. C.; Higgins, R. H.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 851.

(5) Cromwell, N. H.; Matsumoto, K.; George, A. D. *J. Org. Chem.* **1971**, *36*, 272.

(6) Piskov, V. B. *Zh. Obshch. Khim.* **1965**, *35*, 228.

0022-3263/80/1945-4983$01.00/0

Table I

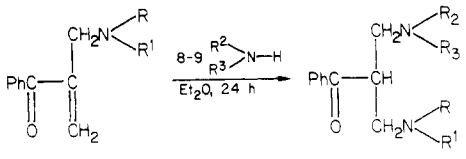


3a-c 5a,b 4a,b

compd	NRR¹	compd	NRR¹	NR²R³	compd	R
a	$NHC(CH_3)_3$	a	$NHC(CH_3)_3$	$NHC(CH_3)_3$	a	$C(CH_3)_3$
b	NC_4H_8O	b	NC_4H_8O	$NHC(CH_3)_3$	b	C_6H_{11}
c	$N(C_3H_7)_2$					

Scheme III and ref 3. If a primary amine is involved in the reaction, subsequent nucleophilic attack of **3** occurs with a second mole of **2a** to yield **4** as the major product. Actually, we have found that unless allylamine **3** contains a sterically hindered alkylamino group (such as *tert*-butyl), it can not be isolated in any quantity. (The reaction, when carried out with cyclohexylamine, yields only product **4b**, even though 1 equiv of **1a** and 1 equiv of cyclohexylamine were employed.) Table I lists the products we have obtained from this series of reactions.

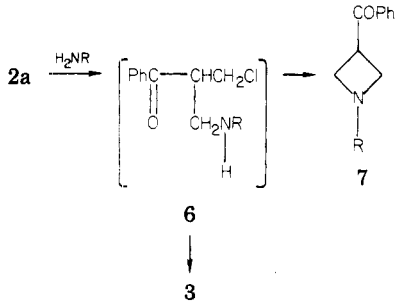
Unlike related keto allyl systems, compounds of form **3** do not undergo amine exchange[5] but rather give a 1,4-addition in the presence of 8–9 molar equiv of a second amine. The Michael addition occurs in excess of 90% yield and is complete in less than 24 h at room temperature. By



3a,b 5a,b

reaction of **3** with a different amine, it is possible to synthesize mixed diamines **5b** in high yield (see Table I).

In no instance was the presence of a 1-alkyl-3-benzoylazetidine **7** observed in these reactions. It must be concluded that the reaction of **2a** with primary amines does not involve a Michael addition to give **6** and then **7** and/or **3**.



Experimental Section

Melting points were determined with a Mel-Temp capillary tube device and are uncorrected. Boiling points are at pressures recorded on a standard Virtis gauge and are uncorrected. Elemental analysis was performed by Micro-Tech Laboratories, Skokie, IL. Infrared spectra were recorded on a Beckman Acu-Lab 4 spectrophotometer. The NMR spectra are reported in δ units with Me_4Si as internal standard, using an A60-D spectrometer. Mass spectra were determined on an AEI MS5076 spectrometer by Dr. Phil Lyon.

Synthesis of 1,3-Dichloro-2-benzoylpropane (1a). This compound is prepared essentially according to the method of Fuson, Ross, and McKeever.[7] A mixture of 45 g of paraformaldehyde, 180 g of acetophenone, 2.0 g of K_2CO_3, and 300 mL of methanol was shaken for 7 days at room temperature and poured into a 1 L of water. The mixture was acidified with HCl (concentrated) and extracted with two portions totaling 500 mL of benzene. The combined extracts were washed with water and dried over anhydrous $MgSO_4$, and solvent was evaporated. The residue was distilled at 145 °C (20 mmHg); 75 g of formaldehyde 2-benzoyltrimethylene acetal was obtained. A 5.0-g sample of the formal was shaken with 50 mL of concentrated HCl, at room temperature, for 24 h. The mixture was then allowed to stand until the oil had solidified. The solid was crystallized twice with *n*-hexane to yield colorless platelets: mp 54–55 °C (lit.[7] mp 56–57 °C); NMR ($CDCl_3$) δ 3.5–4.3 (complex m, 5 H, methine, methylene), 7.1–7.7 (m, 5 H, aromatic); IR ($CDCl_3$) 1690 cm^{-1} (carbonyl); mass spectrum, *m/e* 217 (parent).

Synthesis of 1,3-Dibromo-2-benzoylpropane (1b). The above procedure is repeated, substituting 50 mL of HBr solution with 5.0 g of the formal. Recrystallization from hexane yielded white platelets: mp 53 °C; NMR ($CDCl_3$) δ 3.7 (d, 4 H, J = 3.7 Hz), 3.5–4.2 (m, 1 H, methine), 7.1–7.7 (m, 5 H, aromatic); IR ($CDCl_3$) 1690 cm^{-1} (carbonyl); mass spectrum, *m/e* 306 (parent).

Anal. Calcd for $C_{10}H_{10}OBr_2$: C, 39.25; H, 3.23; Br, 52.22. Found: C, 39.32; H, 3.23; Br, 51.94.

Synthesis of 2-Benzoyl-1-chloro-2-propene (2a). Compound **2a** can be prepared by dissolving 5.0 g of **1a** (0.023 mol) in anhydrous ethyl ether and to this solution an ethereal solution of triethylamine (2.3 g, 0.023 mol) was added dropwise. Stirring for 4 h followed by filtration of triethylamine hydrochloride and evaporation of solvent gave a syrupy white oil. Passage through a column and elution with ethyl acetate gave 3.7 g of a colorless oil (**2a**): IR ($CHCl_3$) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 4.35 (s, 2 H, methylene); 5.6, 6.1 (2 s, 2 H, vinyl), 7.3–7.7 (m, 5 H, aromatic); high-resolution mass spectrum, calcd for $C_{10}H_9OCl$ *m/e* 180.034 18, found *m/e* 180.034 18.

Synthesis of 2-Benzoyl-3-(*tert*-butylamino)-2-propene (3a). (a) From 1,3-Dichloro-2-benzoylpropane (1a). An 8.68-g (0.04 mol) sample of **1a** was dissolved in 50 mL of dry benzene and added dropwise to an ethereal solution of *tert*-butylamine (3.02 g, 0.04 mol) and triethylamine (8.68 g, 0.086 mol) dissolved in ether. The mixture was allowed to react at 20 °C for an additional 4 h and then warmed on a steam bath for an additional 0.5 h. The solution was cooled and the triethylamine salt was removed by filtration. The filtrate was concentrated and the residue extracted with 300 mL of ether. The solution was filtered to remove the remainder of the salt and concentrated to yield a white solid. Recrystallization of the solid from benzene gave 1.5 g of white flakes of the hydrochloride **3a**·HCl, mp 160–161.5 °C. NMR indicated the presence of some additional triethylamine hydrochloride. Passage through a column packed with silica gel and elution with 0.8 ethyl acetate/0.2 acetonitrile gave the free base **3a** as a light yellow oil: IR (CCl_4) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.8 (m, 5 H, aromatic), 5.9, 6.1 (2 s, 2 H, vinyl), 4.4 (s, 2 H, methylene), 3.98 (s, 10 H, *tert*-butyl and NH); mass spectrum, *m/e* 217 (parent).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.37; H, 8.83; N, 6.44. Found: C, 77.83; H, 8.98; N, 6.06.

(7) Fuson, R. C.; Ross, W. E.; McKeever, C. H. *J. Am. Chem. Soc.* **1938**, *60*, 2935.

(b) From 2-Benzoyl-1-chloro-2-propene (2a). A 2.3-g (0.012 mol) sample of **2a** was dissolved in 20 mL of dry benzene and added dropwise to an ethereal solution of *tert*-butylamine (0.876 g, 0.012 mol) and triethylamine (1.21 g, 0.012 mol) dissolved in ether. The mixture was allowed to react at 20 °C for an additional 4 h. The triethylamine salt was filtered and the residue concentrated and extracted with 200 mL of ether. The ether solution was filtered to remove traces of salt and concentrated to give a white solid (0.5 g) which was found to be identical with **3a** as described above.

Synthesis of Bis(2-methylene-3-oxo-3-phenylpropyl)(1,1-dimethylethyl)amine (4a). The filtrate from the above reaction was concentrated to afford a yellow oil which upon standing in the cold gave a pale yellow solid. Recrystallization of this material several times from hexane gave 3.5 g (light yellow crystals): mp 76–77 °C; IR (CCl_4) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.2–7.9 (m, 10 H, aromatic) 5.5, 6.05 (2 s, 2 H, both vinyl), 3.65 (s, 4 H, methylene), 3.15 (s, 9 H, *tert*-butyl); mass spectrum, *m/e* 361 (parent).

Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.88. Found: C, 79.87; H, 7.60; N, 3.81.

Synthesis of 1,3-Bis(*tert*-butylamino)-2-benzoylpropane (5a). A solution of *tert*-butylamine (18 g, 0.246 mol) and triethylamine (5.0 g, 0.024 mol) in benzene was added dropwise to a solution of **1a** (5.0 g, 0.024 mol) in benzene–ether over a 1-h period. The reaction was stirred for 24 h, the amine salt was filtered, and filtrate was evaporated. The yellow oil obtained solidified to a pale yellow solid. Recrystallization gave colorless crystals: 6.0 g (88% yield); mp 65–66 °C; IR ($CHCl_3$) 1680 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.2–7.8 (m, 5 H, aromatic), 3.65 (m, 1 H), 2.95 (d, 4 H, methylene, J = 6.7 Hz), 1.6 (s, 1 H, NH), 1.15 (s, 18 H, *tert*-butyl); mass spectrum, *m/e* 290.1 (parent). Anal. Calcd for $C_{18}H_{30}ON_2$ 0.5 H_2O: C, 72.24; H, 10.36; N, 9.36. Found: C, 72.59; H, 10.25; N, 9.30.

Synthesis of Bis(2-methylene-3-oxo-3-phenylpropyl)-cyclohexylamine (4b). A 5.0-g sample of **1a** (0.024 mol) was dissolved in dry benzene and added dropwise to an ethereal solution of cyclohexylamine (2.23 g, 0.023 mol) and triethylamine (0.046 mol). The mixture was allowed to stir for 4 h. Filtration of the salt and evaporation of the solvent gave a viscous yellow oil which could not be crystallized; yield 8.3 g (89%) of **4b**. TLC, with several solvent combinations, indicated one component: IR ($CDCl_3$) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.2–7.9 (m, 10 H, aromatic), 5.4, 6.1 (2 s, 2 H, both vinyl), 3.8 (s, 4 H, methylene), 1.1–1.9 (br m, 11 H, cyclohexyl); high-resolution mass spectrum, calcd for $C_{26}H_{29}O_2N$ *m/e* 387.2198, found *m/e* 387.2198.

Synthesis of 2-Benzoyl-1-morpholino-2-propene (3b). A 5.0-g sample of **1a** was dissolved in benzene and added dropwise to an ethereal solution of morpholine (2.0 g, 0.023 mol) and triethylamine (4.6 g, 0.046 mol), and the solution was stirred for 4 h. Filtration of the salt and evaporation of the solvent yielded a white solid. Recrystallization from 95% ethanol–ether yielded 3.4 g of **3b**: mp 65–66 °C; IR ($CHCl_3$) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 2.5 (q, 4 H, morpholine ring protons α to N), 3.3 (s, 1 H, methylene), 3.68 (m, 4 H, morpholine ring protons β to N), 5.7, 5.9 (2 s, 2 H, vinyl), 7.3–7.8 (m, 5 H, aromatic); mass spectrum, *m/e* 231 (parent).

Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.99; H, 7.40; N, 5.91.

Synthesis of 1-Morpholino-3-(*tert*-butylamino)-2-benzoylpropane (5b). A 10.0-g sample (0.043 mol) of **3b** was dissolved in ether. To this solution was added 0.43 mol of *tert*-butylamine (31.3 g), dissolved in ether, in a dropwise manner. The solution was stirred for 24 h. At the end of this time the solution was evaporated, yielding a white solid. Recrystallization from petroleum ether several times gave **5b**, the mixed amine: mp 62–63 °C; 10.2 g (75% yield); IR ($CHCl_3$) 1680 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 0.9 (s, 9 H, *tert*-butyl), 1.9–2.0 (br s, NH, 1 H), 2.3 (apparent q, 4 H, morpholine), 2.7–3.0 (m, 4 H, methylene), 3.5 (apparent q, 4 H, morpholine ring protons), 3.8 (m, 1 H, methine), 7.2–7.9 (m, 5 H, aromatic); mass spectrum, *m/e* calcd 305.222 90, found *m/e* 305.222 41.

Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.01; H, 9.27; N, 9.20. Found: C, 71.03; H, 9.28; N, 9.14.

Synthesis of 2-Benzoyl-1-(diisopropylamino)-2-propene (3c). To a solution of **1a** in ether was added 1 molar equiv of diisopropylamine and 2 molar equiv of triethylamine dissolved in benzene. Stirring for 4 h and filtration of the salt gave a green colored solution. Distillation of the oil [bp 116 °C (0.1 mm)] gave a green-yellow oil which quickly crystallized. Recrystallization from petroleum ether yielded green crystals: mp 31 °C; IR ($CHCl_3$) 1660 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 0.6 (d, 12 H, isopropyl methyl), 2.8 (m, 1 H, isopropyl methine), 3.1 (s, 2 H, methylene), 5.7, 5.9 (2 s, 2 H, both vinyl), 7.1–7.8 (m, 5 H, aromatic).

Anal. Calcd for $C_{16}H_{23}ON$: C, 78.33; H, 9.45; N, 5.71. Found: C, 78.37; H, 9.53; N, 5.65.

Acknowledgment. This work was supported by a grant from the National Cancer Institute (grant No. CA-02931) to N.H.C.

Registry No. 1a, 39192-57-9; **1b**, 75030-60-3; **2a**, 58703-02-9; **3a**, 75030-61-4; **3a**·HCl, 75030-62-5; **3b**, 2845-45-6; **3c**, 75030-63-6; **4a**, 75030-64-7; **4b**, 75030-65-8; **5a**, 75030-66-9; **5b**, 75030-67-0; formaldehyde, 50-00-0; acetophenone, 98-86-2; formaldehyde 2-benzoyltrimethylene acetal, 21769-22-2; *tert*-butylamine, 75-64-9; cyclohexylamine, 108-91-8; morpholine, 110-91-8; diisopropylamine, 108-18-9.

Mesoionic Compounds. 52. Attempted Synthesis of the Anhydro-2-hydroxyoxazolo[2,3-*b*]oxazolium Hydroxide System[1]

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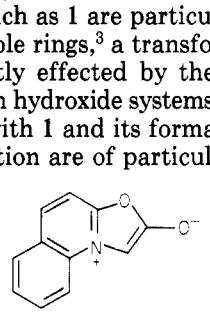
Several recent publications[2] describe a study of the factors controlling the stability of ortho-fused mesoionic ring systems and their ability to undergo cycloaddition reactions, these reactions being particularly useful for ring annelations. In this publication we describe attempts to generate the ortho-fused anhydro-2-hydroxyoxazolo[2,3-*b*]oxazolium hydroxide system **2** and the corresponding benzoxazole system **3** by cyclodehydration of their respective precursors, **4** and **5**. Ortho-fused oxazolium hydroxide systems such as **1** are particularly useful for the annelation of pyrrole rings,[3] a transformation which can also be conveniently effected by the use of the corresponding thiazolium hydroxide systems.[4] The ring system **3** is isoelectronic with **1** and its formation and ability to undergo cycloaddition are of particular interest.



1

Reaction of 2-oxazolidone with ethyl bromoacetate after treatment with NaH/benzene gave the ester **4** (R = COOEt) as a colorless oil (91%). This was hydrolyzed with concentrated HCl at room temperature to the corresponding acid **4** (R = H), obtained as water-soluble, col-

(1) (a) Partial support of this work by U.S. Public Health Service Research Grant CA08495, National Cancer Institute, is gratefully acknowledged. (b) On leave from Yamaguchi University, Japan.

(2) Potts, K. T.; Kanemasa, S. *J. Org. Chem.* **1979**, *44*, 3803, 3806.

(3) Potts, K. T.; Yao, S. *J. Org. Chem.* **1979**, *44*, 977. Potts, K. T.; Chen, S. C.; Szmuszkovicz, J. *Ibid.* **1977**, *42*, 2525.

(4) Potts, K. T.; Choudhury, D. R. *J. Org. Chem.* **1978**, *43*, 2697.

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