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(18) Preliminary findings of P. G. Gassman, R. Yamaguchi, and M. Mullins; P. G. Gassman, R. Yamaguchi, and G. F. Koser, *J. Org. Chem.*, **43**, 4392 (1978).
(19) A methanol/pyridine ratio of 50:1 (v/v) was used. In the absence of pyridine, it was shown that **3** was completely consumed after the passage of less than 0.3 F/mol. Only products resulting from the acid-catalyzed addition of methanol to **3** were observed. The relatively small change in half-wave potential observed in the two different solvents might be interpreted to mean that the solvation of the strained hydrocarbons does not change significantly in going from acetonitrile to methanol.
(20) Satisfactory elemental analyses and spectral data were obtained for all new compounds.

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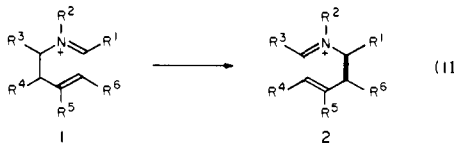
Carbon–Carbon Bond Formation via Directed 2-Azonia-[3,3]-Sigmatropic Rearrangements. A New Pyrrolidine Synthesis

Sir:

The development of versatile methods for forming carbon–carbon bonds under mild conditions is a central objective of synthetic organic chemistry. The 2-azonia-[3,3]-sigmatropic rearrangement[1,2] (eq 1, the C–C bond produced is emboldened) appears to us to be a particularly attractive vehicle for the elaboration of methodology of this type. This reversible[4] carbon–carbon bond-forming reorganization occurs under remarkably mild conditions (typically 100–200 °C below the corresponding Cope rearrangement),[3-6] and a variety of simple methods are available for preparing the starting iminium ion **1**.[7] To be synthetically useful the 2-azonia-[3,3]-sigmatropic rearrangement must be irreversible in the desired direction, and to date essentially all applications have been in benzoheterocyclic systems[5,8] where the rearrangement is driven by aryl conjugation of the product iminium ion (R^3 = aryl). In this communication we outline our preliminary efforts to develop general methods for directing this rearrangement. In particular we report an intramolecular trapping procedure which for the first time allows the less stable iminium ion isomer to be captured in high yield.[9]



The strategy is to incorporate a nucleophilic substituent in such a fashion that it is latent in the starting sigmatropic isomer, but upon rearrangement is unleashed and irreversibly captures the desired product iminium ion (eq 1, R^4 = heteroatom functionality). Within this context we have found that the reaction of aldehydes and salts of 2-alkoxy-3-butenamines affords substituted 3-acylpyrrolidines in a single step, and in excellent yield, eq 2. In a typical experiment a mixture of

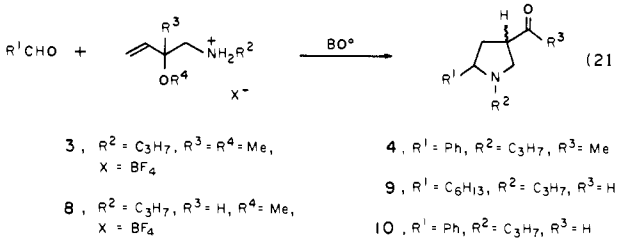
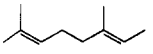


Table I. Preparation of 3-Acetylpyrrolidines According to Eq 2 (R^3 = Me)

entry	R^1	R^2	OR^4	reaction conditions[a] procedure[b]	time, h	isolated yield,[c] %
1	C_6H_5	n-C_3H_7	OMe	A	5	87
2	C_6H_5	n-C_3H_7	OMe	B	24	85
3		n-C_3H_7	OMe	A	24	95
4		n-C_3H_7	OMe	B	24	84
5		n-C_3H_7	OMe	B[d]	24	90
6	n-C_6H_{13}	n-C_3H_7	OMe	A	24	97
7		n-C_3H_7	OMe	A	24	90
8	n-C_6H_{13}		OMe	A	24	95
9	C_6H_5	$C_6H_5CH_2$	OMe	B	24	54
10	C_6H_5	$C_6H_5CH_2$	OMe	B	72	89
11	C_6H_5	$C_6H_5CH_2$	OH	B	24	94
12		$C_6H_5CH_2$	OMe	B	24	57
13		$C_6H_5CH_2$	OH	B	24	95
14		$C_6H_5CH_2$	OH	B	24	91
15		CH_3	OH	B	24	84

[a] A benzene solution of the amine salt (0.6 M) and the aldehyde (1.1 equiv) were heated at reflux for the indicated time. Twenty-four hours was taken as a convenient standard time and many of the reactions were done much sooner. [b] A, the crystalline amine tetrafluoroborate salt was used; B, the free amine plus 0.9 equiv of *d*-10-camphorsulfonic acid was used. [c] All pyrrolidines were a mixture of acetyl epimers.[11] [d] 0.1 equiv of *d*-10-camphorsulfonic acid was employed.

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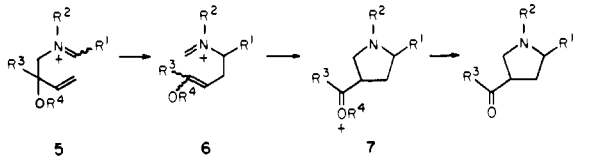
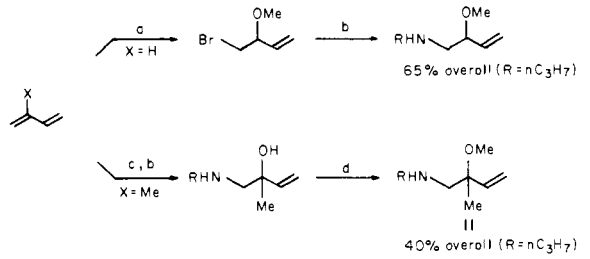
Scheme I



Scheme II



[a] (a) NBS, MeOH; (b) RNH_2 (excess), 25%; (c) NBS, EtO, H_2O; (d) KH, MeI, THF.

benzaldehyde (3.3 mmol) and 2-methoxy-2-methyl-*N*-propyl-3-butenammonium tetrafluoroborate (**3**) was heated for 5 h at reflux in 5 mL of benzene. After the mixture cooled to room temperature, 3 mL of 1 N NaOH was added, and the amine product was isolated by ether extraction and dried (Na_2SO_4). Distillation (bulb to bulb; bath temperature 95 °C; 0.01 mm) afforded 3-acetyl-5-phenyl-1-propylpyrrolidine[10] (**4**, a 1:1 mixture of acetyl epimers) in 87% yield:[11] ν_{max} (film) 1712 cm^{-1}; *m/e* (rel intensity) 231.162 (calcd for $C_{15}H_{21}NO$, 231.162) (8), 202 (100), 188 (23), 154 (12). The scope of this experimentally simple synthesis of substituted pyrrolidines is illustrated in Table I. The reaction succeeds with a variety of aliphatic, aromatic, and heteroaromatic aldehydes and affords uniformly excellent yields. Either the crystalline amine tetrafluoroborate salt (procedure A), or the free amine and 0.9 equiv of anhydrous *d*-10-camphorsulfonic acid (procedure B) may be employed. Entry 5 demonstrates that the reaction according to procedure B may be accomplished with a catalytic amount (0.1 equiv) of acid. The critical oxygen function may be either a methoxyl or hydroxyl group. In cases where a direct comparison can be made (entries 9–13), the reaction was slightly faster and, in the case of furfural higher yielding, when the amino alcohol was employed. Particularly significant are the absence of products resulting from diene cyclization when citral (entry 7) was employed, the high yields obtained with acid-sensitive furfural (entry 13), and the convenient preparation of 3-acetylnicotine (entry 15) by this procedure. The major limitation of the reaction is that the carbonyl component must be an unhindered aldehyde. For example, pivaldehyde and aliphatic ketones were recovered unchanged when heated at reflux in benzene with amine salt **3**. Apparently the neopentyl nature of the amine precludes the formation of the starting iminium ion in these cases.[12]

A mechanistic rationale for the pyrrolidine synthesis of eq 2 is provided in Scheme I. Dehydrative condensation of the starting aldehyde and secondary amine salt gives iminium salt **5**,[7,13] which undergoes [3,3]-sigmatropic rearrangement to **6** under these mild conditions. Intramolecular Mannich ring closure[7] results in the irreversible capture of the rearranged iminium ion isomer **6** to give the oxy carbocation **7**. Hydrolysis ($R^4 = CH_3$) or deprotonation ($R^4 = H$) of **7** yield the acetylpyrrolidine product. It is particularly significant that, for many of the examples summarized in Table I, R^1 was an aryl group, and thus the initially formed iminium ion isomer **5** was the more stable. *The success of the reaction in these cases clearly illustrates the power of this approach for directing the 2-azonia-[3,3]-sigmatropic rearrangement, as it demonstrates that even the less stable sigmatropic isomer may be captured in high yield.*

In extending this methodology to the preparation 3-formylpyrrolidines, we examined the reaction of aldehydes and amine salt **8**. When **8** was allowed to react with heptanal for 24 h in refluxing benzene, the dimethyl acetal of formylpyrrolidine **9** was isolated in 21% yield, together with considerable high molecular weight material. Aldehyde **9** was not detected. The polymerization reaction, which is an obvious complication in this case, was almost totally suppressed, however, when the identical reaction was carried out under acetalizing conditions (3-Å molecular sieves, 1 equiv of methanol) and afforded the dimethyl acetal of **9**[11] in 81% isolated yield. Benzaldehyde was similarly converted to the dimethyl acetal of **10**[11] in 69% isolated yield.

The oxygenated homoallylic amines required for this reaction are available on large scales from isoprene and butadiene as summarized in Scheme II.[14] Amines **11** may also be prepared from 2-methoxy-2-methyl-3-butenal[17] by reductive amination.[18]

The results described here point clearly to the potential of directed 2-azonia-[3,3]-sigmatropic rearrangements in synthesis. Related methodology, stereochemical implications, and applications in the natural products area will be the subject of future disclosures.

Acknowledgment. Support from the National Institutes of Health (NS-12389) is gratefully acknowledged. NMR spectra were determined on an FT NMR spectrometer purchased with the assistance of a National Science Foundation instrumentation grant.

References and Notes

(1) For this notation of [3,3]-sigmatropic shifts, see F. Vögtle and E. Goldschmitt, *Chem. Ber.*, **109**, 1 (1976).
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(4) M. Sainsbury, D. W. Brown, S. F. Dyke, R. G. Kinsman, and B. J. Moon, *Tetrahedron*, **24**, 6695 (1968); M. Sainsbury, S. F. Dyke, D. W. Brown, and R. G. Kinsman, *ibid.*, **26**, 5265 (1970); R. G. Kinsman, S. F. Dyke, and J. Mead, *ibid.*, **29**, 4303 (1973); R. G. Kinsman and S. F. Dyke, *Tetrahedron Lett.*, 2231 (1975).
(5) (a) J. Knabe and N. Rupenthal, *Arch. Pharm. (Weinheim, Ger.)*, **299**, 129 (1966). (b) E. Winterfeldt and W. Franzischka, *Chem. Ber.*, **100**, 3801 (1967); (c) E. Winterfeldt and W. Franzischka, *ibid.*, **101**, 2938 (1968); (d) J. Knabe and H. D. Höltje, *Tetrahedron Lett.*, 2107 (1969); (e) M. Geisel, C. A. Grob, and R. A. Wohl, *Helv. Chim. Acta*, **52**, 2206 (1969); (f) J. A. Marshall and J. H. Babler, *J. Org. Chem.*, **34**, 4186 (1969); (g) H. Rischke, J. D. Wilcock, and E. Winterfeldt, *Chem. Ber.*, **106**, 3106 (1973); (h) C. A. Grob, W. Kunz, and P. R. Marbet, *Tetrahedron Lett.*, 2613 (1975); V. V. Ahmad, K. H. Feuerherd, and E. Winterfeldt, *Chem. Ber.*, **110**, 3624 (1977).
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(7) For reviews of the preparation and chemistry of iminium ions, see H. Böhme and M. Haake in "Iminium Salts in Organic Chemistry, Part 1", H. Böhme and H. G. Viehe, Ed., Wiley, New York, 1976; J. V. Paukstelis in "Enamines", A. G. Cook, Ed., Marcel Dekker, New York, 1969; H. Hellmann and G. Opitz, "α-Aminoalkylierung", Verlag-Chemie, Weinheim, 1960.
(8) Exceptions are described in ref 5e, f, h.
(9) Intramolecular transformations of iminium ions produced in irreversible rearrangements have been reported.[5g]
(10) *Chemical Abstracts* name: 1-(5-phenyl-1-propyl-3-pyrrolidinyl)ethanone.
(11) All new compounds were characterized by ^1H and ^{13}C NMR, IR, and high resolution mass spectra. All yields refer to material of purity >95% as determined by GLC or ^{13}C NMR analysis.
(12) A modification of this methodology which the starting minimum ion is formed from an imine precursor succeeds with ketones and will be the subject of a future report.
(13) Cf. N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).
(14) The reaction of 4-bromo-3-methoxy-1-butene[15] and 1-bromo-2-methyl-3-buten-2-ol[16] with primary amines is regiospecific. Complete experimental details for the preparation of **3** and **8** are available upon request.
(15) J. I, DeGraw, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1156 (1961); A. A. Petrov, *Zh. Obschch. Khim.*, **8**, 208 (1938).
(16) D. R. Dalton and R. M. Davis, *Tetrahedron Lett.*, 1057 (1972).
(17) Prepared from commercially available pyruvaldehyde dimethyl acetal by treatment with (1) CH_2=$CHMgBr$; (2) MeI, KH; (3) 80% HOAc, 80 °C, 5 h, C. Fukaya, unpublished procedure.
(18) Cf. R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**,

2897 (1971).
(19) Camille and Henry Dreyfus Teacher–Scholar Award Recipient, 1976–1981. A. P. Sloan Foundation Fellow, 1975–1977.

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Nucleophilic Substitution in Organomercury Halides by a Free-Radical Chain Process ($S_{RN}1$)[1]

Sir:

The free-radical chain nucleophilic substitution process (reactions 1–3) has been observed in aliphatic[2,3] and aromatic systems[4] and has been labeled $S_{RN}1$.[5] In aliphatic systems all substrates (RX) described to date contain a nitro or *p*-nitrophenyl substituent at the reaction center.[6,7] With the exception of *p*-nitrobenzyl derivatives only tertiary substrates have been successfully employed, generally with the structure $(R)_2C(X)NO_2$, where X = Cl, Br, NO_2, CN, CO_2R, COAr, SO_2R.[8]

$$RX^{-}\cdot \rightarrow R\cdot + X^{-} \quad (1)$$

$$R\cdot + A{:}^{-} \rightarrow RA^{-}\cdot \quad (2)$$

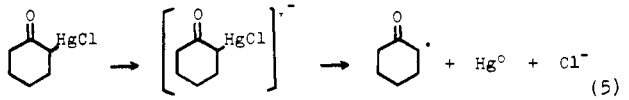
$$RA^{-}\cdot + RX \rightarrow RX^{-}\cdot + RA \quad (3)$$

$$RX + A^{-} \rightarrow RA + X^{-}$$

We have found that primary or secondary alkylmercury chlorides or bromides will participate in the $S_{RN}1$ process with nitronate anions in Me_2SO or DMF (reaction 4).

$$RHgX + R'_2C{=}NO_2^{-} \xrightarrow[N_2]{h\nu} RC(R')_2NO_2 + X^{-} + Hg^{0} \quad (4)$$

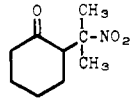
We selected **1** as a substrate for the $S_{RN}1$ process with the idea that the carbonyl group would facilitate the formation of $RX^{-}\cdot$ in reaction 3, and that the radical anion **2** would decompose readily as shown in reaction 5. Reactions of the anions



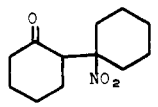
(5)

1 2

of 2-nitropropane or nitrocyclohexane with **1** gave the expected products (**3**) of the $S_{RN}1$ reaction in 60–70% yield when deoxygenated solutions were illuminated with a sun lamp through Pyrex. The reaction showed the characteristics of a



3a, mp 69–70°C

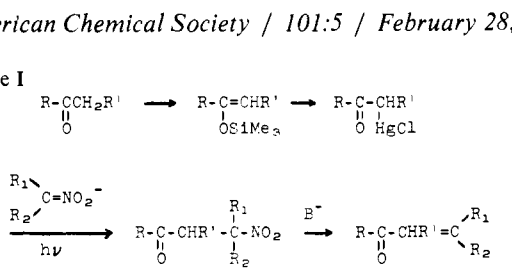


3b, mp 66–68°C

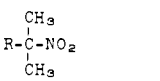
free-radical chain process. Not only was the reaction induced by light, but it was completely inhibited by 5 mol % di-*tert*-butyl nitroxide. The reaction when illuminated started immediately only if the solution was completely deoxygenated. When the deoxygenation was incomplete, inhibition periods were observed.

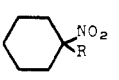
The β-nitro ketones (**3**) readily undergo E_2 elimination of the elements of HNO_2 in basic solution to give the α-alkylidene ketones. The reaction sequence is thus an α-alkylidenation process for a ketone (Scheme I).[9]

Scheme I



Further experiments demonstrated that the carbonyl function is not necessary for the $S_{RN}1$ reaction of an alkylmercury halide. Thus, benzyl-, cyclohexyl-, or *n*-hexylmercury chloride all react with the anion of 2-nitropropane or nitrocyclohexane in a light-catalyzed process at 25 °C to give the coupling products **4** and **5**.[10]





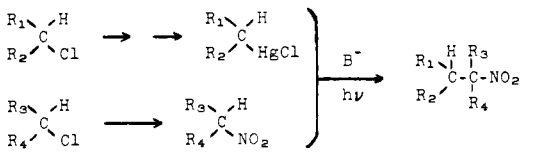
4a, R = benzyl, mp 25° C, 2 h, 99%
4b, R = cyclo-C_6H_{12}, mp 46–47°C, 34 h, 76%
4c, R = n-hexyl, 37 h, 90%
4d, R = 2-methoxycyclohexyl, 47 h, 8:1 ratio of trans and cis isomers

5a, R = benzyl, mp 68.5–69° C, 2 h, 87%
5b, R = cyclohexyl, mp 55–56° C, 60 h, 84%

The rate of the reaction under standard conditions decreases from R = benzyl to R = alkyl. Apparently resonance stabilization of R· formed by reaction 1 is an important consideration. In line with this we have been unable to bring about the coupling of phenyl- or vinylmercury halides with the nitronate anions in reaction 4. Apparently a nitronate anion is required as the anion (A^{-}) in reaction 2 when R· is a simple alkyl radical. The nitro group stabilizes and thus facilitates the formation of $RA^{-}\cdot$ in reaction 2. We have been unable to observe coupling when **1** or other organomercury halides are irradiated in the presence of diethyl methylmalonate anions.

This reaction not only makes available a wide variety of new tertiary nitroalkanes, but when combined with an E_2 elimination of nitrite ions furnishes a wide variety of substituted alkenes from readily available precursors (Scheme II).

Scheme II



In a typical experiment a solution of α-bromomercuricyclohexanone[11] (5.72 mmol, mp 130–131 °C) in 30 mL of DMF was purged of oxygen by a stream of prepurified nitrogen in a 100-mL flask at room temperature. After addition of 6.21 mmol of lithium 2-nitropropanate,[12] the solution was stirred for 1 h at a distance of 8 in. from a 275-W sun lamp. Mercury precipitated in a greenish gray form, which was removed by filtration through Celite after quenching of the reaction mixture with 25 mL of 2% hydrochloric acid. The filtrate was diluted with 100 mL of H_2O and extracted with three 75-mL portions of ethyl ether. The ether extract was washed, dried, and concentrated on a rotary evaporator to give 0.54 g of **3a** (68%): mp 69–70 °C from pentane; bp 98 °C (0.3 Torr); ^1H NMR (CCl_4) δ 1.53 (s, 3 H), 1.62 (s, 3 H), 1.67–2.10 (m, 6 H), 2.16–2.50 (m, 2 H), 3.1–3.4 (m, 1 H).

Acknowledgment. The benzyl- and *n*-hexylmercury chloride were supplied by Professor R. Larock. We thank the National Science Foundation for funds which allowed the purchase of the Finnigan 4023 GC–mass spectrometer used in this work (CHE 76-80362).

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