Reactions of 7-Bromonorcarane with Nucleophiles by the $S_{RN}1$ Mechanism. Novel Nucleophilic Substitutions on the Cyclopropane Ring

Roberto A. Rossi,* Ana N. Santiago, and Sara M. Palacios

Instituto de Investigaciones en Fisicoquímica de Córdoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Sucursal 16-C.C.61-5016 Córdoba, Argentina

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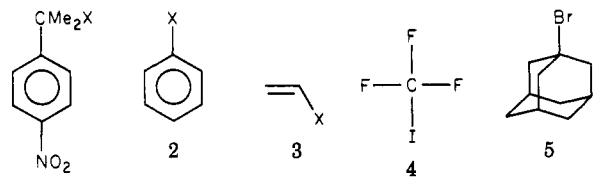
The mechanism of radical nucleophilic substitution, or $S_{RN}1$, is a chain process that has radical and radical anions as intermediates.[1] The main steps of the propagation cycle of this mechanism are fragmentation of the radical anion of the substrate (eq 1), coupling of the radical with the nucleophile (eq 2), and electron transfer from the radical anion of the substitution product to the substrate (eq 3), the step which completes the chain propagation cycle (Scheme I).

Summation of these three steps leads to eq 4, which is a nucleophilic substitution.

Up to now, the main substrates involved in these reactions have been alkyl derivatives activated with an electron-withdrawing group, the first example of this type of nucleophilic substitution discovered in 1966, such as 1,[2] unactivated aryl derivatives 2 (1970),[3] vinyl halides 3 (1976),[4] perfluoroalkyl iodides such as 4 (1977),[5] and bridgehead halides such as 1-bromoadamantane (5) (1982).[6]



1 2 3 4 5

These substrates, except alkyl derivatives activated with electron-withdrawing groups 1, have the same reactivity pattern toward nucleophiles by the S_N1–S_N2 mechanism. All of them either react very slowly or do not react at all by these mechanisms. However, they do react by the radical mechanism of nucleophilic substitution.

Substituted cyclopropanes react by the S_N1 type of nucleophilic substitution, but a disrotatory opening is necessary to assist the departure of the leaving group (electrocyclic process, Woodward–Hoffmann rule).[7] This process has a relatively high activation energy due to the fragmentation of two bonds in a concerted process. When the cyclopropane has the leaving group as well as a substituent at the same carbon atom of the ring that stabilizes the positive charge, it is possible to perform a substitution by the S_N1 mechanism without ring opening.[8]

On the other hand, halocyclopropanes do not usually suffer nucleophilic substitution by the S_N2 type of reaction. An elimination–addition process occurs with strong bases.[9]

From these facts, we thought that halocyclopropanes might react with nucleophiles by the $S_{RN}1$ mechanism of nucleophilic substitution.

Scheme I

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

$$R\cdot + Nu^- \longrightarrow (R\text{-}Nu)^{-\cdot} \quad (2)$$

$$(R\text{-}Nu)^{-\cdot} + RX \longrightarrow R\text{-}Nu + (RX)^{-\cdot} \quad (3)$$

$$RX + Nu^- \longrightarrow R\text{-}Nu + X^- \quad (4)$$

Table I. Reactions of 6 with Nucleophiles in Liquid Ammonia

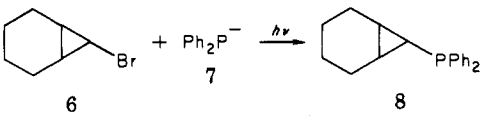
expt	6, M × 10³	nucleophile, M × 10³	irradiation, time, min	yield,[a] % Br⁻	yield,[a] % substitution product
1	4.1	Ph_2P^-, 3.3	10	91	9, 87
2	5.8	Ph_2P^-, 4.8	45	98	9, 94, 52[b]
3	6.0	Ph_2P^-, 4.8	45[c]	5	9, 1
4	5.6	Ph_2P^-, 4.8	180[c]	15	9, *d*
5	6.3	Ph_2P^-, 4.9	45[e]	70	9, 64
6	5.4	Ph_2P^-, 4.8	45[f]	16	9, 6
7	4.4	Ph_2P^-, 3.3	45[c,f]	0	9, 0
8	4.0	Ph_2As^-, 3.3	10	91	11, 90
9	5.7	$^-CH_2COCH_3$, 5.3	120	35	0
10	6.0	$^-CH_2COCH_3$, 6.0	120[c]	0	0

[a] Bromide ion was determined potentiometrically, and the substitution products were determined by GC with internal standard unless otherwise indicated. [b] Isolated yield. [c] Dark reaction. [d] Not quantified. [e] Di-*tert*-butyl nitroxide (10 mol %) was added. [f] 1,4-Dinitrobenzene (20 mol %) was added.

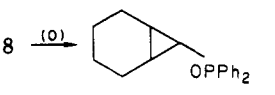
Results and Discussion

7-Bromonorcarane (6) was chosen as a model to study the behavior of halocyclopropanes. These reactions were carried out under photostimulation in liquid ammonia, since light is one of the most frequently used catalysts, with diphenylphosphide ion 7 as the nucleophile, which is one of the most reactive nucleophiles toward aryl[10] and bridgehead radicals.[6]

The photostimulated reaction of 6 with 7 in liquid ammonia afforded 91% of bromide ion in 10 min of irradiation, and (7-norcaranyl)diphenylphosphine (8) was found in 87% yield (eq 5).



6 7 8 (5)



9 (6)

The substitution product 8 was not isolated as such because of its easy oxidation to (7-norcaranyl)diphenylphosphine oxide (9, eq 6) (Table I).

The photostimulated reaction is inhibited by di-*tert*-butyl nitroxide and 1,4-dinitrobenzene, which are very

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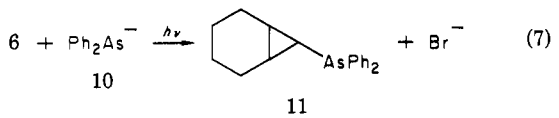
well-known inhibitors in $S_{RN}1$ reactions[1] (70% and 16% of bromide elimination in 45 min of irradiation, respectively). There is a small reaction in the dark (5% yield of bromide ion in 45 min, that increases up to 15% in 180 min). This dark reaction is completely inhibited by 1,4-dinitrobenzene (0% yield of bromide ion in 45 min of reaction).

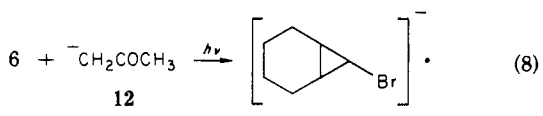
The facts that **6** reacts with **7**, that no arrangement products were formed, that the reaction is strongly catalyzed by light, and that di-*tert*-butyl nitroxide and 1,4-dinitrobenzene inhibited the photostimulated reaction indicate that radical and radical anions are intermediates[11] (Scheme I, RX = **6**, Nu^- = **7**). Similar behavior was found with diphenylarside ion **10** as the nucleophile: there is a photostimulated reaction to give the substitution product **11** (eq 7).



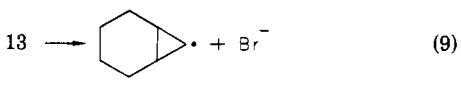
10 11 (7)

Carbanionic nucleophiles such as ketone enolate ions were suitable nucleophiles to react with aryl radicals to give good yields of substitution products by the $S_{RN}1$ mechanism.[1b,c]

In the photostimulated reaction of **6** with acetone enolate ion (**12**), there was 35% bromide elimination, but no substitution product was found. In the dark there was no reaction at all. This behavior is similar to the photostimulated reaction of 1-iodoadamantane with carbanionic nucleophiles where there is dehalogenation when irradiated in the presence of several carbanionic nucleophiles, but no substitution products were formed.[6b] This result suggests that acetone enolate ion **12** transfers one electron to **6** when irradiated to form radical anion **13** (eq 8), which fragments to give cyclopropyl radical **14** (eq 9). This radical **14** does not couple with **12**, it is reduced to norcarane **15** (eq 10) instead.



12 13 (8)



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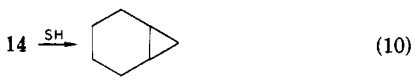

15 (10)

From these results it is concluded that bromocyclopropanes react under irradiation with diphenylphosphide and diphenylarside ions by the $S_{RN}1$ mechanism of nucleophilic substitution, thus adding a new type of substrate to those already known (compounds **2–5**) with a similar reactivity pattern to classical nucleophilic substitution.

Experimental Section

General Methods. NMR spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrometer. Mass spectral measurements were obtained with a Finnigan Model 3.300 mass spectrometer. Gas chromatographic analyses were performed on a Varian Aerograph Series 1400 instrument with a flame ionization detector by using a columm packed with 3% SE-30 on Chromasorb P (1.5 m × 3 mm). Irradiation was conducted in a reactor equipped with four 250-W UV lamps emitting maximally at 350 nm (Philips Model HPT, water refrigerated).

Materials. Diphenylphosphide and diphenylarside ions were prepared from triphenylphosphine (Fluka) and triphenylarsine (Aldrich) and 2 equiv of potassium metal in liquid ammonia, and the amide ion formed was neutralized with *tert*-butyl alcohol.[12] 7-Bromonorcarane was prepared as reported previously[13] and it was purified by vacuum distilation. Di-*tert*-butyl nitroxide was kindly provided by Professor James F. Wolfe.

Photostimulated Reaction of 7-Bromonorcarane with Diphenylphosphide Ion. The photostimulated reaction of diphenylphosphide ion is representative. Into a three-necked, 500-mL, round-bottomed flask, equipped with a cold finger condenser charged with solid CO_2 and ethanol, a nitrogen inlet, and a magnetic stirrer, was condensed 250 mL of ammonia. To the ammonia were added triphenylphosphine (1 mmol) and potassium metal (2 mmol) to form the diphenylphosphide ion, and then *tert*-butyl alcohol (1 mmol) was added. 7-Bromonorcarane (1.2 mmol) was added to this solution and then the solution irradiated for 45 min.

The reaction was quenched by addition of ammonium nitrate in excess, and the ammonia was allowed to evaporate. Water (100 mL) was added to the residue, and the mixture was extracted 3 times with 50 mL of diethyl ether. Triphenylstibine was added as an internal standard to a sample of the ether extract to quantify (7-norcaranyl)diphenylphosphine. In the water layer, bromide ion was determined potentiometrically.

The ether extract was evaporated until all ether was removed, and the residue was recrystallized from petroleum ether–benzene (50/50), and (7-norcaranyl)diphenylphosphide oxide precipitated as a white solid: mp 166–170 °C; ^1H NMR δ 0.9–2.3 (m, 11 H), 7.3–7.9 (m, 10 H); ^{13}C NMR (H noise decoupled) (20.15 MHz) (Cl_3CD) δ 15.4 (C_1), 15.6 (C_6), 19.5 (d, $J_{^{13}C-P}$ = 102.7 Hz), 20.5 ($C_{2,5}$), 22.4 (C_3), 22.6 (C_4), 127.4, 130.9, 131.1 (Ar carbons), 138.1 (d, $J_{^{13}C-P}$ = 103 Hz) (Ar carbon); MS, *m/e* (relative intensity) 296 (67), 253 (43), 215 (19), 202 (100), 183 (25), 155 (22), 125 (18), 94 (9), 77 (61), 65 (12).

Photostimulated Reaction of Diphenylphosphide Ion with 7-Bromonorcarane in the Presence of Inhibitors. The procedure was similar to that for the previous reactions, except that in experiment 5 (Table I) 10 mol % of di-*tert*-butyl nitroxide was added and in experiment 6 (Table I) 20 mol % of 1,4-dinitrobenzene was added.

Photostimulated Reaction of 7-Bromonorcarane with Diphenylarside Ion. The procedure was similar to that used for previous reactions, except that the irradiation time was 10 min. The residue was column chromatographed on silica gel and eluted with benzene as a liquid: ^1H NMR δ 0.8–2.2 (m, 11 H), 7–7.5 (m, 10 H); MS, *m/e* (relative intensity) 324 (48), 229 (41), 226 (52), 171 (48), 167 (50), 152 (100), 129 (38), 95 (98), 67 (60).

Photostimulated Reaction of 7-Bromonorcarane with Acetone Enolate Ion. Acetone enolate ion was prepared insitu by acid–base reaction with sodium *tert*-butoxide. The reaction was analyzed by gas chromatography and no product was detected.

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Registry No. **6**, 1121-39-7; **7**-K, 15475-27-1; **8**, 90245-79-7; **9**, 87944-11-4; **10**-K, 21498-51-1; **11**, 90245-80-0; **12**, 71695-00-6.

(11) Although this mechanism involves a one-electron transfer reaction in the initiation step, it is different from the one proposed for the reaction of bromomethylcyclopropane with dimethylphosphide (*J. Org. Chem.* **1977**, *42*, 3247), since the latter is not a chain reaction.

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