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PHOTOSTIMULATED REACTIONS OF NEOPENTYL HALIDES WITH NUCLEOPHILES BY THE $S_{RN}1$ MECHANISM

ESTEBAN R. N. BORNANCINI, SARA M. PALACIOS, ALICIA B. PEÑÉÑORY
AND ROBERTO A. ROSSI*
Instituto de Investigaciones en Fisicoquimica de Córdoba (INFIQC), Departmento de Quimica Orgánica, Facultad de Ciencias Quimicas, Universidad Nacional de Córdoba, C.C. 61, Suc. 16, 5016 Córdoba, Argentina

ABSTRACT

The photostimulated reaction of neopentyl halides with different nucleophiles by the $S_{RN}1$ mechanism of nucleophilic substitution has been studied. Neopentyl halides do not react with carbon nucleophiles, diethylphosphite, diphenylphosphonite and azide ions, but they react with arsenide and selenide ions. The photostimulated reaction of neopentyl bromide with diphenylarsenide ions gave only the straightforward substitution product neopentyldiphenylarsine. On the other hand, the photostimulated reaction of bromobenzene with dineopentyl arsenide ions gave three arsines: dineopentylphenylarsine, neopentyldiphenylarsine and triphenylarsine. Neopentyl chloride reacts under irradiation with diphenylphosphide ions giving good yields of the substitution product.

Radical nucleophilic substitution, or $S_{RN}1$, is a well known process,[1] and several different types of substrates react by this mechanism. The main steps of the propagation cycle are outlined in Scheme 1.

SCHEME 1

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

$$R^{\cdot} + Nu^{-} \longrightarrow (RNu)^{\cdot-} \tag{2}$$

$$(RNu)^{\cdot-} + RX \longrightarrow RNu + (RX)^{\cdot-} \tag{3}$$

$$(RNu)^{\cdot-} + RX \longrightarrow RNu + R^{\cdot} + X^{-} \tag{1,3}$$

In aliphatic systems with no low lying π^* molecular orbitals, such as bridgehead halides,[2] perfluoroalkyl iodides,[3] halocyclopropanes[4] and neopentyl halides,[5] the radical anion $(RX)^{\cdot-}$ may not be formed at all as intermediate,[6] and equations (1) and (3) occur simultaneously (equation (1, 3)).

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*Author for correspondence

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Recently we have reported[5] the photostimulated reaction of neopentyl bromide with benzenethiolate, benzeneselenate, diphenylphosphide and diphenylarsenide ions by the $S_{RN}1$ mechanism of nucleophilic substitution. Also, the reaction of lithium propiophenone with 1-iodo-2,2-dimethyl-5-hexene, a neopentyl halide with a radical probe has been reported, and it was proposed that this reaction occurs by a single electron transfer (SET) mechanism.[7]

We now report the photostimulated reaction of neopentyl halides with other nucleophiles in order to know the scope and limitations of these substrates in $S_{RN}1$ reactions.

RESULTS AND DISCUSSION

The photostimulated reaction of neopentyl bromide **1** with carbanionic nucleophiles, such as acetone enolate ion, picolyl anion, cyanomethyl anion, the enolate ions of acetyl morpholine, diethyl malonate and nitromethane gave only a small dehalogenation reaction of **1**, but no substitution products were found. This behavior parallels the behavior of bridgehead halides, where only dehalogenation with reduction and the formation of dimeric products were formed in the photostimulated reaction with carbanions nucleophiles. Neopentyl bromide in photostimulated reactions with diethyl phosphite, diphenylphosphonite and azide ions did not react either (Table 1).

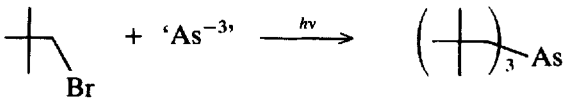
Table 1. Photostimulated reaction of neopentyl halides with nucleophiles in liquid ammonia

Expt	X	Neo-X[a] (M × 10^2)	Nu^-	(M × 10^2)	Irradiation Time (min)	Yield, % X^-	Products (%)
1	Cl	(0·40)	Ph_2P^-	(0·40)	225	76	Ph_2NeoPO (69)
2	Br	(0·80)	Carbanions[b]		180	4–29	—
3	Br	(0·80)	$(EtO)_2PO^-$	(0·64)	90	8	—
4	Br	(0·80)	N_3^-	(0·66)	90	4	—
5	Br	(0·80)	‘As^{-3}’	(0·56)	120	48	Neo_3As (33)
6[c]	Br	(0·80)	Ph_2As^-	(0·64)	10	90	$NeoPh_2As$ (82)
7[d]	Br	(0·55)	$(Neo)_2As^-$	(0·17)	30	[e]	Neo_2PhAs (16%) $NeoPh_2As$ (29%) Ph_3As (19%)
8	I	(1·28)	‘Se^{-2}’	(2·21)	150	[e]	NeoSeSeNeo (83) NeoSeNeo (10)
9	I	(0·13)	—	—	240	0·3	—

[a] Neo = neopentyl;
[b] Carbanions derived from acetone, picoline, acetylmorpholine, acetonitrile, diethylmalonate and nitromethane were formed by acid–base reaction in liquid ammonia in *ca.* 0·008–0·010 M/l;
[c] See Reference 5;
[d] Bromobenzene;
[e] Not quantified.

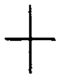
The nucleophiles ‘As^{-3}’[8] and ‘Se^{-2}’[9] are formed by reaction of the metals with sodium in liquid ammonia, and they react under photostimulation with aromatic halides[8,9] and 1-haloadamantanes[2b] to give good yields of arsines and selenides.

In the photostimulated reaction of **1** with ‘As^{-3}’ **2** in liquid ammonia, we found that Br^- ions were formed in 48% yield while tri(neopentyl)arsine **3** was isolated in 33% yield (equation (4)).

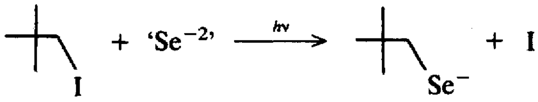


1 **2** **3**

(4)

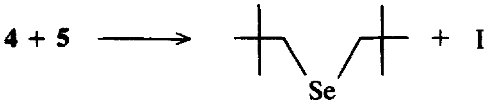

= neopentyl $[(CH_3)_3CCH_2^-]$

In the photostimulated reaction of neopentyl iodide **4** with 'Se^{-2}' in liquid ammonia, we found after oxidation of the reaction product high yields of dineopentyl diselenide **7**, together with a small amount of dineopentyl selenide **6** as by product, which was obtained by the reaction of **4** with the nucleophile **5** formed in the reaction (equations (5–7)). There was no reaction at all during the irradiation of **4** in liquid ammonia in the absence of nucleophiles (Table 1).



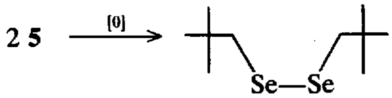
4 **5**

(5)



6

(6)



7

(7)

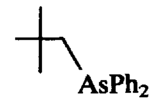
The photostimulated reaction of several haloaromatic compounds, such as *p*-halotoluenes **8** with diphenylarsenide ions **9** gave the expected *p*-tolyldiphenylarsine **11**, together with triphenylarsine **10**, di(*p*-tolyl)phenylarsine **12** and tri(*p*-tolyl)arsine **13** (equation (8)).[10]

$$\underset{\mathbf{8}}{\mathrm{ToX}} + \underset{\mathbf{9}}{\mathrm{Ph_2As^-}} \xrightarrow{h\nu} \underset{\mathbf{10}}{\mathrm{Ph_3As}} + \underset{\mathbf{11}}{\mathrm{ToPh_2As}} + \underset{\mathbf{12}}{\mathrm{To_2PhAs}} + \underset{\mathbf{13}}{\mathrm{To_3As}} \qquad (8)$$

To = *p*-tolyl

This reaction occurs by the $S_{RN}1$ mechanism and the scrambling of phenyl rings was ascribed to the fragmentation of the radical anion intermediates formed in the coupling of radicals with **9**. However, in the photostimulated reaction of aromatic substrates with low lying π^* molecular orbitals, such as 4-chlorobenzophenone, no scrambled products were found. This result was explained in terms of the radical anion intermediate formed in the coupling of 4-benzoylphenyl radical with **9**, the odd electron is located in the low lying π* molecular orbital of the 4-benzoylphenyl moiety, which prevents the C—As bond fragmentation.[11]

In the photostimulated reaction of **1** with **9** only the straightforward substitution product **14** is formed (equation (8)).[5]

$\mathbf{1} + \mathbf{9} \xrightarrow{h\nu}$  $+ \mathrm{Br}^-$ (9)

14

This lack of scrambled products cannot be ascribed to the formation of a stable π* radical anion $\mathbf{14}^{\cdot -}$ in the coupling of neopentyl radicals **15** with **9** in order to prevent the fragmentation of the C—As bonds. Another possibility to explain the formation of only **14**, is that the fragmentation rate of the C—As bonds are quite different if the C—As bond is aliphatic or aromatic. If the fragmentation rate is faster in the aliphatic C—As bond, **14** is the only product that can be formed (equation (11)).

$$\mathbf{1}^{\cdot -} \longrightarrow \underset{\mathbf{15}}{\mathrm{Neo}^{\cdot}} + \mathrm{Br}^- \qquad (10)$$

$$\begin{tikzcd}
\mathbf{15} + \mathbf{9} \arrow[r, shift left] \arrow[r, leftarrow, shift right, "k_f\mathrm{Neo}"'] & \underset{\mathbf{14}^{\cdot -}}{(\mathrm{NeoAsPh_2})^{\cdot -}} \arrow[r, shift left, "k_f\mathrm{Ph}"] \arrow[r, leftarrow, shift right] \arrow[d, "\mathbf{1}"] & \mathrm{NeoPhAs}^- + \mathrm{Ph}^{\cdot} \\
& \mathbf{14} + \mathbf{1}^{\cdot -} &
\end{tikzcd} \qquad (11)$$

Neo = neopentyl

If k_fNeo >> k_fPh no scrambled products would be formed since the radical anion $\mathbf{14}^{\cdot -}$ has only two competitive reactions: regression to starting **15** and **9**, or electron transfer to **1** to form the substitution product **14**.

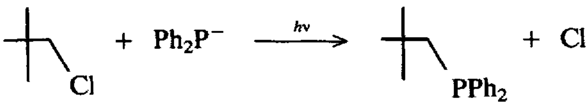
In order to demonstrate if the required condition is that k_fNeo >> k_fPh, we studied the photostimulated reaction of bromobenzene with dineopentylarsenide ions **16**, and we found dineopentylphenylarsine **17** (16% yield), neopentyldiphenylarsine **13** (29% yield) and triphenylarsine **10** (19% yield) (equation (12)).

$$\mathrm{PhBr} + \underset{\mathbf{16}}{\mathrm{Neo_2As}^-} \xrightarrow{h\nu} \underset{\mathbf{17}}{\mathrm{Neo_2PhAs}} + \underset{\mathbf{13}}{\mathrm{NeoPh_2As}} + \underset{\mathbf{10}}{\mathrm{Ph_3As}} \qquad (12)$$

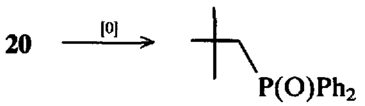
The fact that in equation (9) only one product is formed, and in equation (12) three arsines were formed, is indicative that the rate of fragmentation of the C—As bonds of the radical anion intermediate $\mathbf{14}^{\cdot -}$ is faster when the arsenic atom is bonded to the aliphatic moiety than when it is bonded to the aromatic moiety.[12]

1-Chloroadamantane reacts sluggishly under photostimulation with diphenylphosphide ions in liquid ammonia by the $S_{RN}1$ mechanism,[2a]* whereas other bridgehead chlorides, such as 1-chlorobicyclo[2.2.2]octane,[14] 1-chlorobicyclo[2.2.1]heptane[15] and 4-chlorotricyclane[15] do not react at all in the same experimental conditions. The lack of reactivity was ascribed to the increase in strain energy of the bridgehead halides, making their reduction potentials more negative as the strain increased. As neopentyl chloride has no strain energy, it was desirable to know what the reactivity of alkyl chlorides without strain energy in $S_{RN}1$ reactions was, although neopentyl chloride is a *primary* alkyl chloride, and the bridgehead chlorides are *tertiary* alkyl chlorides.

We found out that in the photostimulated reaction of neopentyl chloride **18** with diphenylphosphide ions **19**, 76% of chloride ions were formed in 225 min. of irradiation, along with 69% yield of the substitution product, isolated as the oxide **21** (equations (13, 14)).



18 **19** **20** (13)



21 (14)

These results show that indeed, the reactivity of neopentyl chloride is higher than 1-chloroadamantane as well as other bridgehead chlorides, and the decrease of the reactivity is due to the strain energy of the bicyclic compounds.[15]

EXPERIMENTAL SECTION

General methods

NMR spectra were recorded on a Varian T-60 nuclear magnetic resonance spectrophotometer. Mass spectral measurements were obtained with a Finnigan Model 3300 mass spectrometer and gas chromatographic analyses were performed on a Varian Aerograph series 1400 instrument with a flame ionization detector by using a column packed with 3% SE 30 on Chromosorb P (0·5 mt × 3 mm) or 5% OV 17 on Chromosorb P (1·5 mt × 3 mm). Irradiation was conducted in a reactor equipped with four 250 W μv lamps emitting maximally at 350 nm (Philips Model HPT, water refrigerated).

Materials

Neopentyl bromide was synthesized by the reaction of neopentyl alcohol (Aldrich) with Ph_3PBr_2 in DMF.[16] Traces of DMF (1–2%) were present in the neopentyl bromide employed.

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*The photostimulated reaction of 1-chloroadamantane with diphenylphosphide ion gave, after 4 hr of irradiation, 36% yield of substitution product. This yield was not increased in liquid ammonia-*t*-butylamine (7:3) as solvent.[13]

Neopentyl iodide was prepared by treating neopentyl tosylate with KI in DMF.[17] Neopentyl chloride (Aldrich) was used as received. Selenide and arside ions were prepared from the metals by the previously reported procedure.[8,9] Diphenylphosphide ions were prepared from triphenylphosphine (Sigma) and two equivalents of sodium metal in liquid ammonia, and the amide ion formed was neutralized with one equivalent of *tert*-butyl alcohol.[2a] Diphenylphosphonite ion was prepared from triphenylphosphine oxide and two equivalents of sodium metal in liquid ammonia, the amide ion was neutralized with *t*-butyl alcohol.[18] Acetone, acetyl morpholine and 2-picoline were purified by distillation and stored over molecular sieves according to standard procedures. Diethyl phosphite ion was prepared from the acid with K metal. Sodium azide, nitromethane and diethyl malonate were used without further purification. The enolate ions of acetone, diethyl malonate and nitromethane were prepared by acid–base reaction of potassium *t*-butoxide (formed *in situ* from *t*-butyl alcohol and K metal catalyzed with $FeCl_3$).[19] The carbanions derived from 2-picoline, acetonitrile and acetyl morpholine were generated by acid–base reaction of their conjugated acid with potassium amide (obtained *in situ* by reaction of K metal in ammonia catalyzed by $FeCl_3$).

Photostimulated reactions of neopentyl chloride with diphenylphosphide ions

The following procedure is representative of these reactions: into a three-necked 500 ml round-bottomed flask, equipped with a cold finger condenser charged with dry ice–ethanol, a nitrogen inlet and a magnetic stirrer, was condensed 250 ml of ammonia previously dried under nitrogen. Triphenylphosphine (1 mmol) and sodium metal (2 mmol) was added to the ammonia to form diphenylphosphide ions, and then *tert*-butyl alcohol (1 mmol) was added to neutralize the amide ions formed. Neopentyl chloride (1 mmol) was added and the solution irradiated for 225 minutes. The reaction was quenched by the addition of excess ammonium nitrate and the ammonia was then allowed to evaporate. Water (100 ml) was added to the residue and the mixture was extracted with diethyl ether. The chloride ions in the aqueous phase were determined potentiometrically (76% yield). The ether extract was quantified by GLC with Ph_3Sb as internal standard compared with an authentic sample.

Photostimulated reaction of neopentyl bromide with potassium arsenide

Neopentyl bromide (0·5 ml, 4·0 mmol) was added to an orange solution of potassium arsenide in dry liquid ammonia freshly prepared from arsenic metal (79·1 mg, 1·05 mmol) and K metal in excess (271 mg, 6·9 mmol), and *t*-butyl alcohol (0·5 ml, 5·3 mmol),[8] and then the solution was irradiated for three hours. After quenching the reaction with ammonium nitrate in excess, the ammonia was allowed to evaporate under a nitrogen atmosphere. The residue was extracted with methylene chloride (previously degassed) and immediately evaporated trying to avoid the oxidation of the trineopentylarsine. The arsine was stored under nitrogen atmosphere until it was used in the reaction with bromobenzene (trineopentylarsine was isolated in 33% yield). The alkaline salts were extracted with water and the Br^- ions were determined potentiometrically (48% yield based on the arsenic metal used). Trineopentyl arsine: Mass spectrum, *m/e* relative intensity) 288 (14); 218 (13); 147 (9); 141 (9); 125 (5); 111 (9); 97 (19); 85 (33); 71 (100); 57 (100); ^{1}H-NMR was run for the trineopentylarsine oxide, (DMSO-d_6, TMS) δ 1·07 (27 H, s); 3·04 (6 H, s).

Photostimulated reaction of bromobenzene with potassium dineopentylarside

To a 250 ml of freshly distilled ammonia and under a nitrogen atmosphere, trineopentylarsine (122·7 mg, 0·43 mmol) and an excess of potassium metal (154 mg, 3·94 mmol) were added until we could get the solution to remain blue for one hour. Then, *t*-butyl alcohol (0·04 ml, 0·43 mmol) was added, and the final color of the solution was yellow. To this solution bromobenzene was added (0·145 ml, 1·38 mmol) and irradiated for 30 minutes. After quenching the reaction with ammonium nitrate, the ammonia was allowed to evaporate, and the reaction was extracted as described above. The ether extract was analyzed by GLC. Triphenylarsine and neopentyldiphenylarsine were quantified by the internal standard method compared with authentic samples, and dineopentylphenylarsine was quantified considering equal molar response to neopentyldiphenylarsine. Almost the same results were obtained in a duplicate run.

Photostimulated reaction of neopentyl bromide with carbanions, diethylphosphite and azide ions

The nucleophiles were prepared as described in Materials. The procedure was similar to those previously described (Br^- ions were titrated in the aqueous solution, see Table 1). No products derived from coupling of neopentyl radicals with these nucleophiles (GLC and mass spectra of the ether solutions) were found.

Photostimulated reaction of neopentyl iodide with disodium selenide

Neopentyl iodide (0·43 ml, 3·20 mmol) was added to a solution of disodium selenide in ammonia, freshly prepared from selenium metal (436 mg, 5·52 mmol) and sodium metal (270 mg, 11·7 mmol), and then the solution irradiated for 150 min. After quenching the reaction with ammonium nitrate, the ammonia was allowed to evaporate, and the reaction was extracted as described above. The iodide ion was determined potentiometrically in the water layer and the ether extract was evapored. The residue was column chromatographed on silica gel and eluted with petroleum ether. The products isolated were dineopentylselenide (20·7 mg, 10·2%) and dineopentyldiselenide (114·5 mg, 83%). Dineopentylselenide: liquid isolated by column chromatography. Mass spectrum, *m/e* (relative intensity) 222 (2·0); 220 (2·0); 85 (7·3); 83 (4·2); 71 (100); 69 (8·3); 67 (3·1); 57 (24·5); 55 (12·0); 53 (4·2); 51 (26); 43 (67); 41 (14·6). ^{1}H-NMR (CCl_4, TMS), δ 1·00 (9 H, s), 3·0 (2 H, s). Dineopentyldiselenide: liquid isolated by column chromatography. Mass spectrum, *m/e* (relative intensity) 305·54 (0·6); 304·00 (2·34); 301·98 (7·1); 299·98 (6·75); 297·88 (4·08); 295·98 (1·6); 233·92 (2·0); 231·92 (6·6); 229·92 (6·0); 227·92 (4·0); 225·90 (1·5); 71·12 (100); 43·04 (86). ^{1}H-NMR (CCl_4, TMS), δ 0·90 (9 H, s), 3·5 (2 H, s).

Photostimulated reaction of neopentyl iodide in liquid ammonia

Neopentyl iodide (0·43 ml, 3·20 mmol) was added to a 250 ml of dry liquid ammonia under nitrogen, being the solution irradiated for 4 hours. Ether was added to the solution and the ammonia was allowed to evaporate. Finally distilled water was added to the residue and in the aqueous solution iodide ions was determined potentiometrically (0·3% yield).

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