Stereospecific Addition of Singlet Phenylnitrenium Ion to Some Alkenes. Reactions of Phenyl Azide with Alkenes in the Presence of Trifluoroacetic Acid

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Stereospecific addition to some alkenes of a singlet phenylnitrenium ion, generated from phenyl azide in the presence of trifluoroacetic acid, gives aziridinium ions; this addition is followed by ring-opening reactions of aziridinium ions.

Nitrenium ions are of great interest in organic chemistry and biochemistry. We have reported the presence of an ethoxycarbonylnitrenium ion[1] and a phenylnitrenium ion[2] in the decomposition in acetic acid of ethyl azidoformate and phenyl azide, respectively, but aromatic *N*-substitution by these species did not occur, possibly because of a competing reaction with the neighbouring acetate anion or solvent. In the presence of trifluoroacetic acid (TFA),† instead of acetic acid, however, aromatic *N*-substitution by these nitrenium ions occurs and yields ethyl *N*-arylcarbamates[3] and diarylamines.[4]

The metabolically activated forms of some carcinogens have been postulated to be arylnitrenium ions capable of reaction with bionucleophiles.[5] The formation of covalent adducts between arylamine cations and nucleophilic sites in DNA is generally considered to be an initiating factor in the induction of tumours.[6,7]

Studies on the reactivity of nitrenium ions may thus be very valuable for following tumour development and for the synthesis of anti-cancer drugs. The present work is the first investigation of the intermolecular addition of nitrenium ions to alkenes, although it is known that nitrenium ions[8] or amino-radical species[9] may be added to double bonds in an intramolecular reaction.

The reaction of phenyl azide with cyclohexene in the presence of TFA gave *trans*-1-(phenylamino)-2-(trifluoroacetoxy)cyclohexane (**1**), 3-(phenylamino)cyclohexene (**2**),

Table 1. Reaction of phenyl azide with cyclohexene in the presence of TFA at room temp. for 1 day.

[Azide]/M	[c-C_6H_{10}][b]/M	TFA, % v/v	Yield,[a] % (1)	(2)	(3)
0.47	4.9	45	63	11	10
0.46	1.0	85	43	9	9
0.32	0.33	94	28	6	6

[a] Yield based on azide decomposed. [b] Cyclohexene.

† Using trifluoromethanesulphonic acid instead of TFA, aromatic *N*-substitution was also observed. Details will be reported in the near future.

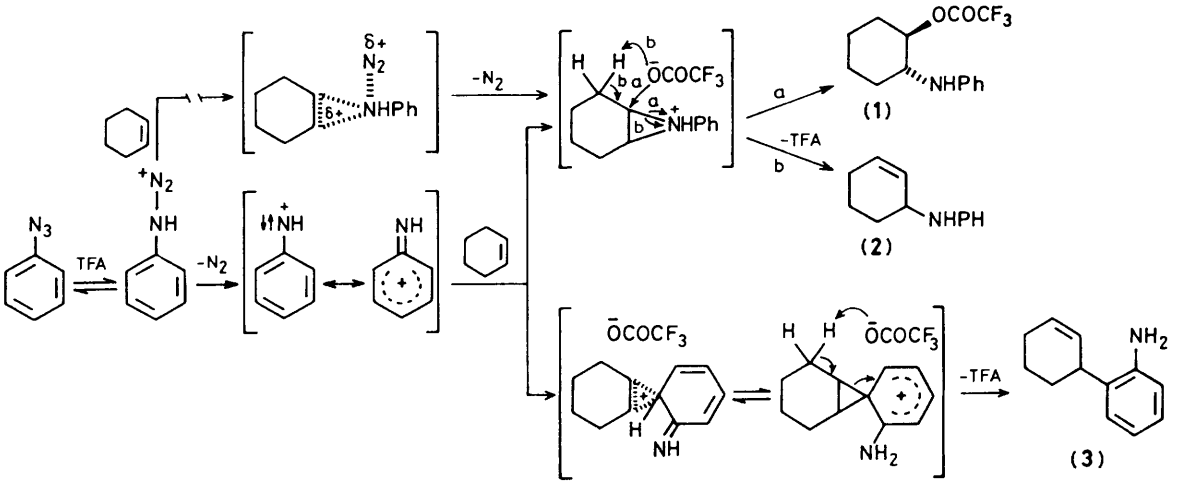
and 3-(2-aminophenyl)cyclohexene (3) (Table 1). Reactions with *cis*- and *trans*-4-methylpent-2-ene instead of cyclohexene are shown in Scheme 2 and the results are given in Table 2.

We have previously reported that the decomposition of phenyl azide in benzene–TFA proceeds *via* an azide conjugate acid, forming a phenylnitrenium ion.[4] For the reaction with alkenes, there are two possible pathways at first sight (see Scheme 1); one involves addition of the phenylnitrenium ion to the alkene, and the other involves an S_N2-like attack of the alkene on the azide conjugate acid. If the reaction occurs *via* the latter route, decomposition of the azide in cyclohexene–TFA rather than benzene–TFA should be

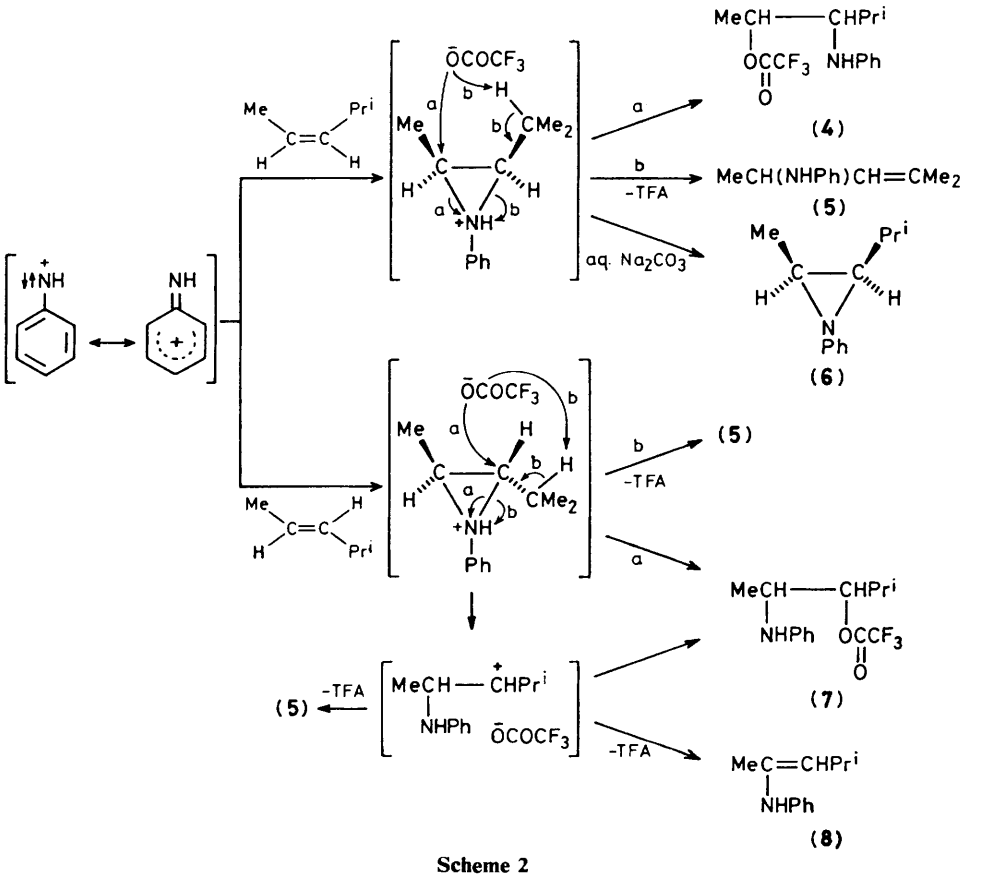
Table 2. Reactions of phenyl azide (0.45 M) with *cis*- and *trans*-4-methylpent-2-enes in the presence of TFA at room temp. for 1 day.

[Alkene]/M	TFA, % v/v	Yield,[a] % (4)	(5)	(6)	(7)	(8)
3.7[b]	48	48	9	6	—	—
1.6[b]	75	20	7	14	—	—
3.7[c]	48	—	18	—	54	4
1.6[c]	75	—	12	—	34	2

[a] Yield based on azide decomposed. [b] *cis*-4-Methylpent-2-ene was used. [c] *trans*-4-Methylpent-2-ene was used.



Scheme 1



Scheme 2

accelerated because cyclohexene is more nucleophilic than benzene. The first-order rate constant for this decomposition in cyclohexene (50% v/v)–TFA (50% v/v) solution at 21.0 °C, $k_1 = 9.0 \times 10^{-5}$ s^{-1}, is, however, slightly lower than in benzene (50% v/v)–TFA (50% v/v) solution at 21.0 °C, $k_1 = 1.2 \times 10^{-4}$ s^{-1}‡ which rules out the S_N2 reaction. Thus the conjugate acid of azide must spontaneously lose a dinitrogen molecule to give the phenylnitrenium ion.

Since the preferential *trans*-addition affords (**1**) and since the addition giving (**4**) and (**7**) is regiospecific, the singlet phenylnitrenium ion§ probably adds stereospecifically to alkenes to form aziridinium ions, followed by ring-opening reactions. This nicely corresponds to the results for ring-opening reactions of some 1-ethoxycarbonylaziridines by acetic acid.[10] Attack of the trifluoroacetate anion on the backside of the breaking C–N bond of the aziridinium ion (step a in Schemes 1 and 2) may give (**1**), (**4**), or (**7**), while proton-abstraction by the anion (step b in Schemes 1 and 2) would produce (**2**) or (**5**).¶

According to ^{13}C-n.m.r. and g.l.c. analyses, (**7**) was a mixture of two diastereoisomers but (**4**) involved no diastereoisomers. The yield of (**5**) was much greater from *trans*-4-methylpent-2-ene than from the *cis*-isomer. These facts would mean that (**8**) and some of both (**7**) and (**5**) are formed by S_N1 ring-opening reactions of an aziridinium ion (see Scheme 2).

Compound (**3**) might be produced *via* an intermediate** arising from attack of cyclohexene on the positive ring-position of the phenylnitrenium ion (Scheme 2).

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‡ The charge-transfer interaction between TFA and cyclohexene is stronger than that between TFA and benzene, so that the formation of the azide conjugate acid may be suppressed in the presence of cyclohexene rather than benzene.

§ If the reaction involves the triplet phenylnitrenium ion, the *cis*-isomer of (**1**) together with (**1**) should be produced, and a regiospecific addition giving (**4**) and (**7**) could not be expected.

¶ The isolation of the *cis*-aziridine (**6**) [which is relatively stable as the aziridinium ion under the reaction conditions (ref. 10)], after neutralization of the reaction mixture with Na_2CO_3, supports the formation of aziridinium ions as intermediates. *N*-Cyclohexylidenephenylamine, which is a tautomer of 1-(phenylamino)cyclohexene, was not formed from cyclohexene, and (**8**) was not detected in the reaction with *cis*-4-methylpent-2-ene. These both indicate that the reaction with cyclohexene or *cis*-4-methylpent-2-ene does not proceed *via* the S_N1 ring-opening mentioned below. The compound (**2**) was not formed from (**1**) under the reaction conditions without the azide.

** A similar intermediate may be proposed from the fact that 1-(2- and 4-aminophenyl)hex-2-enes were isolated from the reaction of the azide with hex-1-ene in the presence of TFA (unpublished result). However, we could not isolate the *para*-isomer of (**3**).