Reactions of Nitroarenes with Grignard Reagents. General Method of Synthesis of Alkyl-nitroso-substituted Bicyclic Aromatic Systems

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Conjugated addition of Grignard reagents to nitro-compounds provides a new method of synthesis for alkyl-nitroso-derivatives in the naphthalene, quinoline, indole, benzothiophen, benzoxazole, and benzothiazole series. The mechanism is discussed. Detailed mass spectra as well as ^{1}H n.m.r. spectra are reported for unknown nitroso-compounds.

NITROARENES [1] as well as nitroalkanes [2] are reported to undergo 1,2-addition at the nitro-function by Grignard reagents; subsequent reduction of the adducts formed either gives *N*-substituted hydroxylamines [3] or amines.[4] Conversely, conjugated addition has been described for systems such as nitro-olefins [5] or polynitrobenzenes.[6]

We recently reported a new example [7] of the latter kind of reaction by obtaining substantial amounts of nitroso-derivatives, alkylated in the aromatic nucleus, from reactions between nitrobenzothiazoles and alkylmagnesium halides in tetrahydrofuran (THF) at room temperature. Further detailed investigation [8] of the alkylation process has led us to postulate that this reaction proceeds by conjugated addition of RMgX to a nitro-compound, (1), the cyclohexadiene-type adduct formed, (2), undergoing subsequent decomposition to (3) following addition of Lewis acids and water to the reaction mixture (see Scheme). Such reactivity with respect to normal 1,2-addition could be a result of the stabilizing influence of a condensed ring on the adducts (3), rather than the particular feature of the thiazole nucleus. With this in mind we have attempted to extend our reaction to a general method of synthesis and, in so doing, have assessed the reactivities of alkylmagnesium halides on various hetero- and homo-cyclic benzo-condensed aromatic nitro-compounds.

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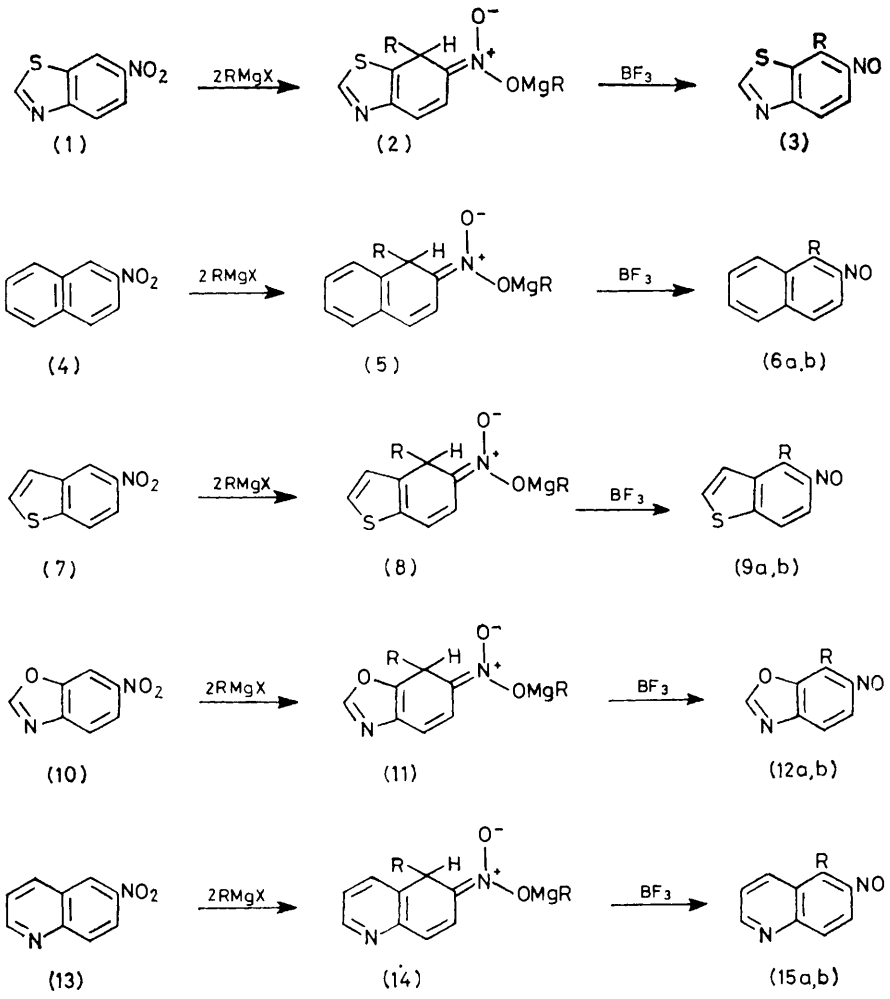
[6] T. Severin and M. Adam., *Chem. Ber.*, 1964, **97**, 186; T. Severin and M. Adam, *ibid.*, 1963, **96**, 448.

[7] G. Bartoli and G. Rosini, *Synthesis*, 1976, **4**, 270.

[8] G. Bartoli, R. Leardini, M. Lelli, and G. Rosini, *J.C.S. Perkin I*, 1977, 884.

RESULTS AND DISCUSSION

Two typical Grignard compounds (BuMgBr and $Ph[CH_2]_2MgBr$) were allowed to react at room temperature in tetrahydrofuran (THF) with the following substrates: 2-nitronaphthalene (4), 5-nitrobenzothiophen (7), 6-nitrobenzoxazole (10), 6-nitroquinoline (13), and 5-nitroindole (16). Each experiment was performed with the same procedure [8] used for the benzothiazole system, which utilizes BF_3 to decompose the adducts formed from interaction between RMgX and the nitro-compounds. Results are summarized in Table 1. With the reaction of 6-nitroquinoline with $Ph[CH_2]_2MgBr$ as the only exception, all the other reactions were successful and led to the formation of nitroso-derivatives. For benzothiophen, naphthalene, and benzoxazole substrates yields were either excellent or comparable to those obtained with benzothiazole. Although results were less satisfactory for indo*Soc.*, 1967, quinoline systems, this may be attributed, at least in part, to instability of the products. Nitroso-derivatives of quinoline did, in fact, spontaneously decompose even when kept in the dark at low temperature. Only small quantities of (15a) were isolated. In this case we could not rule out the possibility that there might have been a competitive addition reaction [9] of RMgX to the C=N bond, since accurate analysis of the reaction mixture was prevented by substantial amounts of tar. Indole derivatives are relatively more stable, so that their yields were higher.



SCHEME

With nitroindole as the only exception, the RMgX molar concentration must be twice that of the substrate in order for these reactions to proceed to completion. Moreover, when the reactions were carried out with a substrate : RMgX molar ratio of 1 : 1, unchanged starting material was recovered almost exclusively.

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These findings are in good agreement with the hypothesis that cyclohexadiene-type adduct formation follows a two-stage mechanism:[10] in the first stage RMgX and substrate interact to yield a 1 : 1 co-ordination complex, when a *para*-position with respect to nitro-group is available for nucleophilic attacks of RMgX (see 7-nitrobenzothiazole).[8]

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TABLE 1

Reactions of some nitro-compounds with RMgX

Substrate	R	Product	M.p. (°C) *	Yield † (%)	Eluant ‡
(4)	Bu	(6a)	61—62	52—63	CH–EA (19 : 1 v/v)
	$Ph[CH_2]_2$	(6b)	74—75	61—73	CH–B (1 : 1 v/v)
(7)	Bu	(9a)	65—66	58—67	CH–EA (9 : 1 v/v)
	$Ph[CH_2]_2$	(9b)	63—64	56—65	CH–EA (9 : 1 v/v)
(10)	Bu	(12a)	35—37	51—62	CH–EA (4 : 1 v/v)
	$Ph[CH_2]_2$	(12b)	89—90	48—57	CH–EA (4 : 1 v/v)
(13)	Bu	(15a) §	50 *	9—15	CH–B(4 : 1 v/v)
	$Ph[CH_2]_2$	Tar			
(16)	Bu	(20a) §	~80 *	17—27	CH–EA (4 : 1 v/v)
	$Ph[CH_2]_2$	(20b) §	~50 *	18—29	CH–EA (4 : 1 v/v)

* Crystallized from n-hexane. † Yield ranges for three separate reactions. ‡ CH = Cyclohexane, EA = ethyl acetate, B = benzene. § Large amounts of decomposition products.

TABLE 2

Analytical and spectroscopic data of some alkyl-nitroso-derivatives of naphthalene, benzothiophen, benzoxazole, quinoline, and indole systems

Compound	Analyses * C	H	N	$\nu_{N=O}$ (KBr) † (cm^{-1})	λ_{max} ($CHCl_3$) [nm (ε)]	δ
(5a)	78.84	7.09	6.57	1 260(TD)	765(30)	0.75—2.15 and 4.05—4.35 (7 H and 2 H, m, n-C_4H_9), 6.00—6.15 and 6.95—7.10 (1 H and 1 H, AB system, H-3, H-4, *J* 8.5 Hz), 7.10—7.35 and 7.90—8.10 (3 H and 1 H, m, H-5, H-6, H-7, H-8) ($CDCl_3$)
	79.01	7.11	6.71			
(6b)	82.73	5.79	5.36	1 408(CD)	765(35)	2.90—3.20 and 4.30—4.60 (2 H and 2 H, m, CH_2CH_2), 5.95—6.10 and 6.95—7.10 (1 H and 1 H, AB system, H-3, H-4, *J* 8.5 Hz), 6.70—6.80 (5 H, m, C_6H_5), 7.10—7.35 and 7.85—8.10 (3 H and 1 H, m, H-5, H-6, H-7, H-8) ($CDCl_3$)
	83.32	5.68	5.43	1 390		
(9a)	65.74	5.98	6.39	1 410(CD)	755(14)	0.8—2.25 and 5.10—4.35 (7 H and 2 H, m, n-C_4H_9), 6.15—6.30 and 7.40—7.55 (1 H and 1 H, AB system, H-6, H-7, *J* 8.5 Hz), 7.50—7.60 and 7.75—7.85 (1 H and 1 H, AB system, H-2, H-3, *J* 6.0 Hz) (CCl_4)
	66.19	5.82	6.28	1 390		
(9b)	71.90	4.90	5.24	1 470(M)	755(16)	3.05—3.35 and 4.35—4.65 (2 H and 2 H, m, CH_2CH_2), 6.15—6.30 and 7.40—7.55 (1 H and 1 H, AB system, H-6, H-7, *J* 8.5 Hz), 7.05—7.15 (5 H, m, C_6H_5), 7.40—7.50 and 7.65—7.75 (1 H and 1 H, AB system, H-2, H-3, *J* 6.0 Hz) (CCl_4)
	72.03	4.98	5.31			
(12a)	64.69	5.92	13.72	1 465(M)	765(37)	0.63—2.30 and 3.65—4.20 (7 H and 2 H, m, n-C_4H_9), 6.05—6.20 and 7.15—7.30 (1 H and 1 H, AB system, H-4, H-5, *J* 8.5 Hz), 8.10 (1 H, s, H-2) (CCl_4)
	64.51	6.10	13.85			
(12b)	71.41	4.80	11.11	1 460(M)	760(34)	3.10—3.40 and 4.20—4.50 (2 H and 2 H, m, CH_2CH_2), 6.25—6.40 and 7.35—7.50 (1 H and 1 H, AB system, H-4, H-5, *J* 8.5 Hz), 7.05—7.15 (5 H, m, C_6H_5), 8.15 (1 H, s, H-2) (CCl_4)
	72.01	5.01	11.31			
(15a)	72.87	6.59	13.08	1 480(M)	760(—)	0.75—2.20 and 4.15—4.50 (7 H and 2 H, m, n-C_4H_9), 6.30—6.45 (1 H, d, H-7, $J_{7,8}$ 9.0 Hz), 7.2—7.40 (1 H, dd, $J_{3,2}$ 4.0 Hz, $J_{3,4}$ 8.2 Hz), 7.50—7.65 (1 H, d, H-8, $J_{6,5}$ < 1 Hz), 8.45—8.60 (1 H, m, H-4, $J_{4,2}$ 2.0 Hz), 8.70—8.80 (1 H, dd, H-2) ($CDCl_3$)
	73.56	6.81	13.14			
(20a)	71.26	6.98	13.85	1 470(M)	730(22)	0.75—2.25 and 3.90—4.25 (7 H and 2 H, m, n-C_4H_9), 6.25—6.40 and 6.90—8.25 (1 H and 3 H, half AB system and m, H-6 or H-7, $J_{6,7}$ 8.5 Hz and H-2, H-3, H-7 or H-6), 11.5 (1 H, br, NH) [$(CD_3)_2CO$].
	69.70	6.72	14.01			
(20b)	76.78	5.64	11.19	1 460(M)	725(35)	3.10—3.40 and 4.20—4.50 (2 H and 2 H, m, CH_2CH_2), 6.25—6.40 and 6.95—7.50 (1 H and 8 H, half AB system and m, H-6 or H-7 and C_6H_5, H-2, H-3, H-7 or H-6, $J_{6,7}$ 8.5 Hz), 11.2 (1 H, br, NH) [$(CD_3)_2CO$]
	76.10	5.81	11.29			

* Upper line required, lower line found. † M = monomer; TD = *trans*-dimer; CD = *cis*-dimer.

which is readily attacked by further RMgX to give the adduct.

This mechanistic pattern is also supported by the fact that 1,6-addition is competitive with 1,4-addition kind have been postulated[11] from kinetic studies and observed[12] in solution by spectroscopic techniques in reactions between RMgX and various ketones. Follow-

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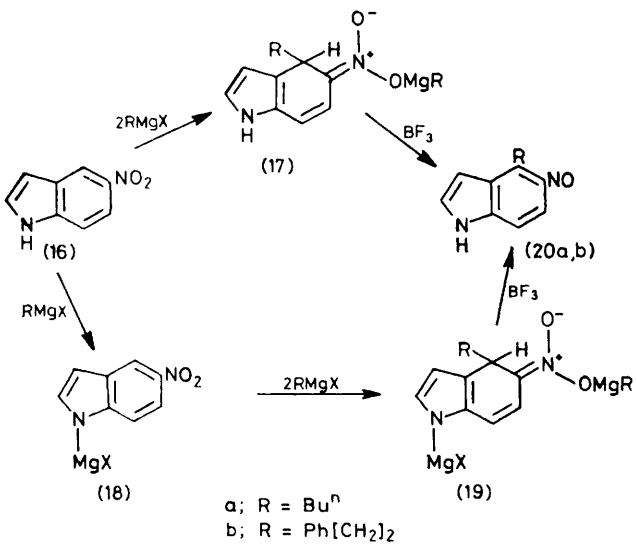
[11] E. C. Ashby, R. Duke, and H. M. Newman, *J. Amer. Chem. Soc.*, 1967, **89**, 1964.

[12] S. G. Smith, *Tetrahedron Letters*, 1963, 409.

ing these ideas we have described adducts as depicted in the Scheme.

A larger excess of RMgX (2.5—3.0 molar) is required in reactions of nitroindole. The high acidic property of hydrogen in position 1 of the indole system,[13] in all likelihood, leads to competitive metallation reaction in this position, thus rendering the reactant unavailable



for the main reaction. This interpretation is supported by the fact that the reaction time is considerably longer in this case (see Experimental section), as required by the lower reactivity of the species (18). However, since under the normal conditions (substrate : RMgX, 1 : 2 molar ratio) reaction leads to significant amounts of nitroso-compound along with unchanged starting material, we cannot exclude that, in part, the process follows the normal one *via* the intermediate (17).

Regioselectivity of Alkylation.—As shown in the Scheme, high regioselectivity of alkylation was observed. Both the proposed mechanism and the nucleophilic character of the entering alkyl group would predict that either of the *ortho* positions with respect to the nitro-group should be equally open to attack. In previous studies, however, we discovered that the condensed ring could exert an influence on the orientation of alkylation in the benzene nucleus. Thus, 5- and 6-nitrobenzothiazoles [8] undergo alkylation exclusively in the 4- and 7-positions, since attack in these positions only gives adducts that retain the aromaticity of the thiazole ring. The present results confirm these interpretations, since orientation of alkylation is strictly dependent upon the stability of adducts (5), (8), (11), (14), and (17), irrespective of the nature of the condensed ring.

TABLE 3

Mass spectra of some alkyl-nitroso-derivatives: relative intensities of major peaks

Compound	6a	6b	9a	9b	12a	12b	20a
Mol. wt.	213	261	219	267	204	252	250
Ion							
M	56.0	12.5	72.0	15.0	55.0	12.0	17.0
M — OH	50.5	100	73.5	100	60.0	100	100
$M - C_2H_5$	15.0		37.5		41.0		
$M - C_3H_7$	100		100		100		
(M — OH)-HCN					65.5	40.5	14.5
$M - C_4H_9$	55.5		68.5		44.0		
$M - C_7H_7$		6.5		7.0		9.5	8.5
C_7H_7	8.0	46.0	14.5	37.0	18.5	47.5	40.0
C_6H_5	12.0	10.0	22.5	16.0	46.5	6.5	20.5
C_5H_5	5.5	15.5	8.0	29.0	20.5	13.5	20.0

Characterization of the Products.—Common analytical procedures were used to identify the alkyl-nitroso compounds (see Table 2). All nitroso-compounds are present in solution as monomers,[14] as indicated by absorption near 750 nm in their u.v. spectra. Some of them are present as dimers [15] in the solid state: the i.r. data enable us to attribute the *trans*-form to (6a) and the *cis*-form [16] to (6b) and (9a). Their exact structures were deduced by ^{1}H n.m.r. spectroscopy, which shows an AB system in the region of the aromatic hydrogens for all compounds; J values (*ca.* 3.5 Hz) are typical for the *ortho* protons of a benzene nucleus. Individual signals constituting the AB system could be attributed precisely only for 6-nitroso-5-butylquinoline. In fact the presence in its spectrum of a detectable long-range coupling (*ca.* 1 Hz) between H-8 and H-4 enabled us to assign the resonance at δ 7.60 to H-8 and then the resonance at δ 6.40 to H-7.

Mass spectra do confirm this attribution. Previously we found a profound fragmentation [8] of *ortho*-alkylnitrosobenzothiazoles due to OH loss from the molecular ion. Mass data reported in Table 3 are in good agreement with these previous results and demonstrate that this kind of fragmentation is general for *o*-alkylnitroso-compounds.

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[16] N. B. Colthup, L. H. Daly, S. B. Wiberly, 'Introduction to Infrared and Raman Spectroscopy', Academic Press, London, 1964.

EXPERIMENTAL

I.r., u.v., ^{1}H n.m.r., and mass spectra were recorded with a Perkin-Elmer 257, a Perkin-Elmer 402, a JEOL 60 MHz (tetramethylsilane as internal standard), and a JEOL MS-D 100 instrument, respectively.

2-Nitronaphthalene and 5-nitroindole are commercial products (EGA Chemie); 6-nitroquinoline, 5-nitrobenzothiophen, and 6-nitrobenzoxazole were prepared as described by Filippi,[17] Boswell,[18] and Roussos [19] respectively. THF was purified by refluxing it over sodium metal and distilling it under a nitrogen atmosphere; it was stored over sodium wire and distilled over lithium aluminium hydride before use; n-butyl bromide and 2-phenyl ethyl bromide and boron trifluoride–diethyl ether complex were commercial products (Schuchart).

General Procedure.—In all experiments we were able to adopt a general experimental procedure which is very close to that previously reported for the benzothiazole system.

In the reactions of 6-nitroquinoline the aqueous mixture was saturated with ammonium chloride before extraction with CH_2Cl_2. As mentioned in the Discussion, in the reactions of 5-nitroindole the experiments were carried out with RMgX : substrate, 2.5—3.0 : 1 mol ratio. All operations were carried out as far as possible from the light.

Reactions, products, yields, some physical data (m.p.), and eluant mixtures used in chromatographic separation are reported in Table 1.

Elemental analysis, i.r., u.v., and ^{1}H n.m.r. data of unknown alkyl-nitroso compounds are collected in Table 2. The ε value for compound (15a) is not reported owing to its fast decomposition in solution. Mass spectra are presented in Table 3. Data for compounds (15a) and (20a) could not be recorded because of their fast decomposition in the spectrometer cavity. Even compound (20b) is susceptible to decomposition so that in its spectrum the magnitude of some peaks could be due, in part, to the fragmentation of products arising from its decomposition.

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