JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 455–466 (1998)

Rate enhancement of 1,3-dipolar cycloaddition of *N*-methylindole: the singular role of Grignard reagents

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Received 13 June 1997; revised 23 September 1997; accepted 29 September 1997

ABSTRACT: The reactions of 2-*N*-methylindolyl and 2- and 3-benzo[*b*]thiophenyl anions with nitrile oxides and nitrilimines were performed in order to investigate whether the use of anionic dipolarophiles modifies a classical 1,3-dipolar cycloaddition. When lithium compounds were used as bases, the heterocyclic anions invariably acted as nucleophilic species; in contrast, when a Grignard reagent was employed, the *N*-methylindole gave cycloaddition products with an extraordinary rate enhancement. The hypothesis that *N*-methylindole and ethylmagnesium bromide give an adduct much more reactive than *N*-methylindole itself was supported by the results of a theoretical investigation. The structure and electron distribution of the adduct were determined by *ab initio* calculations and compared with those of known Grignard complexes with nitrogen ligands. The performance of different basis sets was tested. The quantum theory of atoms in molecules was used to determine atomic charges and to describe the nature of bonds in terms of the properties of the electron density at the bond critical points. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 1,3-dipolar cycloaddition; *N*-methylindole; Grignard reagents; rate enhancement

INTRODUCTION

It is well known that the kinetics and the regioselectivity of 1,3-dipolar cycloaddition reactions are strongly affected by the nature of the substituent present on the dipolarophilic species; steric and electronic effects are extensively documented in the chemical literature.[1]

Our original plan was to investigate the reactions of 1,3-dipoles with anionic dipolarophiles carrying a negative charge on the unsaturated dipolarophilic system; our aim was to check whether the negative charge could behave as an unconventional, small and strong σ and π electron donating substituent. Of course, the anionic unsaturated system could also react with 1,3-dipoles as a nucleophile rather than as a dipolarophile. However, if it could act, at least in part, as a dipolarophilic species, it should be possible to verify how the negative charge modifies a classical 1,3-dipolar cycloaddition: the charge could change not only the kinetics but also the regioselectivity of the cycloaddition.

Therefore, the 2-*N*-methylindolyl and 2- and 3-benzo[*b*]thiophenyl anions were chosen for a preliminary investigation; in the latter case the different localization of the charge in position 2 and 3 could direct the regioselectivity of the process. The stable 3,5-dichloromesitonitrile oxide and a number of nitrilimines were chosen as dipoles, because their reactions with neutral *N*-methylindole and thianaphthene are documented in the literature.

The reactions of *N*-methylindole with nitrile oxides[2] and nitrilimines[3] are known to give cycloaddition products **1** and **3** in low yields together with minor amounts of open-chain oximes **4** and hydrazones **2**. The reaction is sluggish, requiring days or even months at room temperature.

It has also been reported that melt benzo[*b*]thiophene[4] reacts with the 3,5-dichloromesitonitrile oxide (ArCNO) (**5**) to give both the isomeric cycloaddition products, in low yields, after 10 h of heating at 80 °C, whereas it is unreactive towards nitrilimines.

In the course of our experimental investigations, some results of the reactions of *N*-methylindole with 1,3-dipoles, in the presence of a Grignard reagent as a base, suggested the intermediacy of an adduct between the heterocyclic substrate and the organomagnesium compound, rather than the formation of an anionic species. A theoretical investigation was undertaken to substantiate

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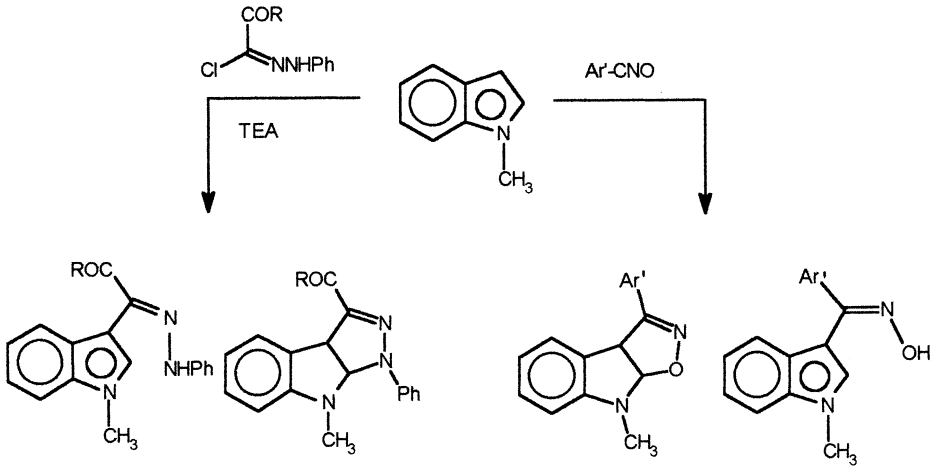
Contract/grant sponsor: CNR; *contract grant number:* CT94.01635.CT03; *contract grant number:* CT95.01302.CT03.

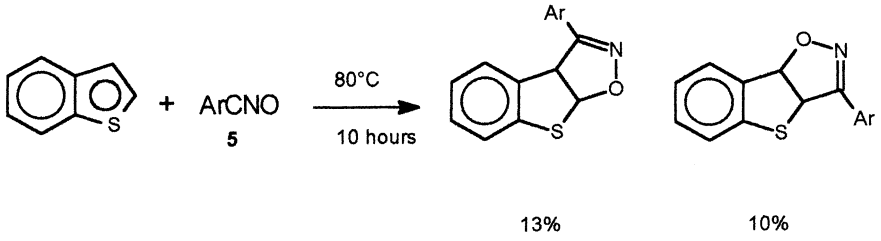
 CCC 0894–3230/98/070455–12 $17.50



2 **1** **3** **4**

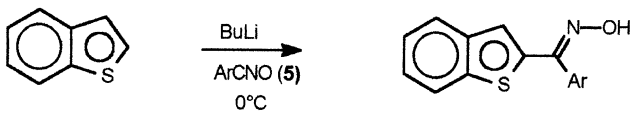
R	time	temp, °C	yield% 2	yield% 1
OEt	1 month	25	8	35
Me	1 month	25	13	36

Ar'	time	temp. °C	yield% 3	yield% 4
Ph	48h	25	19	5
2,4,6-triMeC$_6$H$_2$	1 month	25	62	-



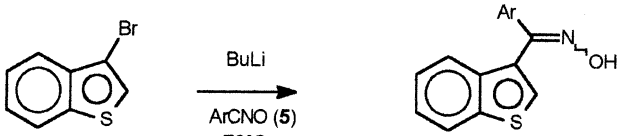
13% 10%

this hypothesis, and the effects of complexation on *N*-methylindole structure, electronic distribution and reactivity were investigated.



6

56%



$\mathbf{7}_{a,b}$

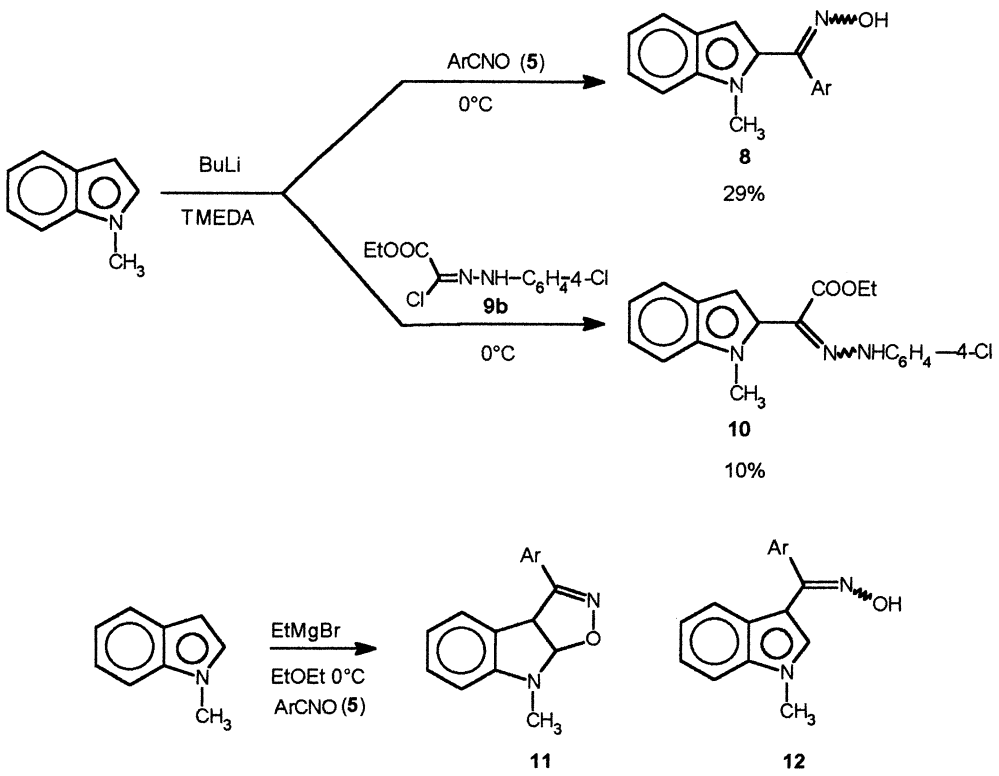
60%

RESULTS AND DISCUSSION

Experimental results

2-Benzo[*b*]thienyllithium, directly prepared from thianaphthene (butyllithium, diethyl ether, 40 °C), immediately reacted with 3,5-dichloromesitonitrile oxide (**5**) at 0 °C to give the oxime **6** in 56% yield. The 3-benzo[*b*]thienyllithium, prepared from 3-bromothianaphthene (butyllithium, diethyl ether, −70 °C, analogously reacted with **5** to give the diastereoisomeric oximes **7a** and **b** in 60% overall yields.

A parallel behaviour was shown by 2-*N*-methylindolyllithium (*N*-methylindole, butyllithium, *N,N,N′,N′*-tetramethylethylenediamine, diethyl ether, 40 °C), which rapidly reacted with **5** at 0 °C to give the oxime **8** in 29% yield. The same anion reacted with the nitrilimine prepared from the chlorohydrazone **9b** at 0 °C to give the open-chain hydrazone **10**. Quenching with deuterium oxide of the lithium compound demonstrated that



lithiation of the heterocyclic ring is quantitative and fully regioselective.

Structural assignments of the reaction products were unequivocally made on the basis of analytical and spectral data.

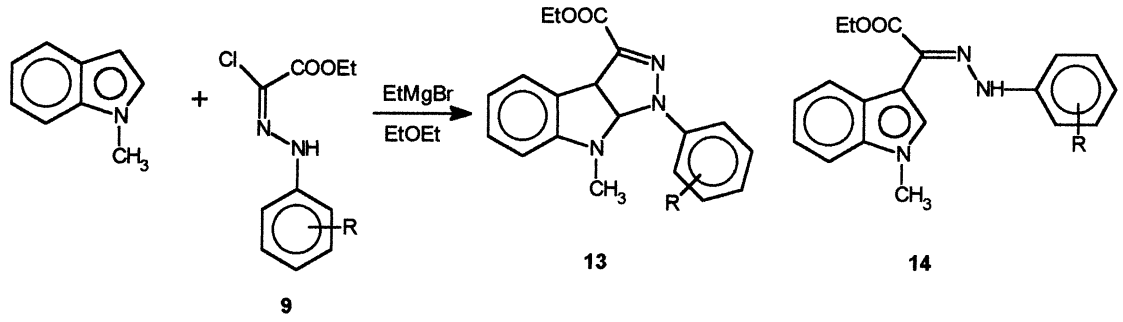
These results demonstrate that the heterocyclic lithium compounds behave as nucleophilic rather than dipolarophilic species, no trace of cycloaddition products having been detected. The hypothesis that open-chain oximes **6**–**8** and hydrazones **10** would result from a base-induced ring opening of initially formed cycloadducts contrasts with the documented stability of these isoxazolines and pyrazolines toward basic reagents[2,3] and with the experimental data reported hereafter. We tried to muffle the nucleophilic character of the anion by changing the hard lithium with the softer magnesium cation. For this purpose, the *N*-methylindole was refluxed (30 min) with ethylmagnesium bromide in diethyl ether, then treated with **5** at 0 °C. We observed the very fast disappearance of **5** and the formation of the expected cycloaddition product **11**, together with some oxime **12** and by-products resulting from direct reaction of the Grignard reagent with **5**. Overall yields calculated on the nitrile oxide **5** are low (*ca* 15%), but well reproducible.

We extended the reaction of the *N*-methylindole and ethylmagnesium bromide to nitrilimines, which were produced *in situ* from halohydrazones **9a**–**g** by using one equivalent excess of the Grignard reagent at 0 °C. We could isolate the cycloaddition products **13a**–**d** starting from substrates **9a**–**d**. No cycloaddition products were detected using chlorohydrazones **9e**–**g**. The presence of electron-donating substituents on the aromatic ring of the hydrazonic moiety inhibits the cycloaddition process. Reactions are very fast and the final state is reached in few minutes. Isolation yields of **13** are low (6–15%), some open-chain hydrazones **14a**–**d** and the expected tetrazines (from nitrilimine dimerization) always being produced.

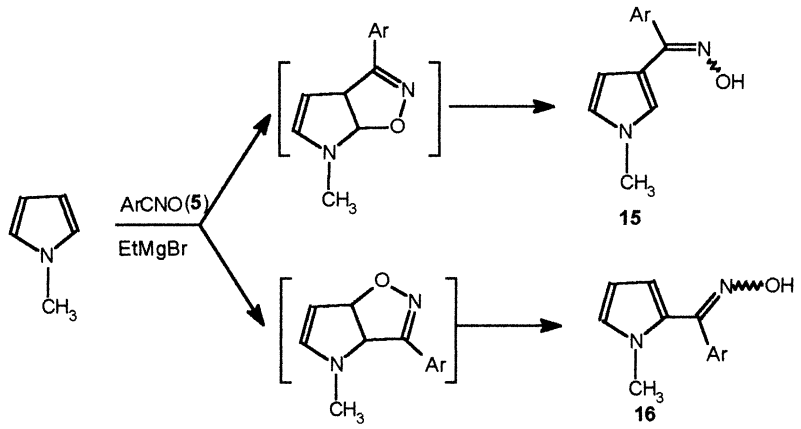
Different results were obtained in the case of benzo[*b*]thiophene: no reaction products containing both the thianaphthene and the dipolarophile moieties were isolated. In this case degradation of the dipolarophilic species is much faster than cycloaddition.

The most relevant feature of the reactions of the *N*-methylindole with **5** and **9** in the presence of ethylmagnesium bromide is the extraordinary rate enhancement of the cycloaddition process produced by the Grignard reagent. Cycloaddition products **11** and **13a**–**d** are not detectable when *N*-methylindole and nitrile oxide **5** or chlorohydrazones **9a**–**d** and triethylamine are stored at 0 °C in diethyl ether solution for weeks. Furthermore, isolation of cycloaddition products with the nitrile oxide **5** and nitrilimines, generated *in situ* from **9,** in the presence of a Grignard reagent, is even more interesting considering that ethylmagnesium bromide istantaneously transforms **5** and **9** into unreactive by-products at 0 °C.

The last observation concerns the regioselectivity of the cycloaddition, which is opposite to that expected for



a: R = H; **b**: R = 4-Cl; **c**: R = 4-NO_2; **d**: R = 3-NO_2; **e**: R = 4-Me; **f**: R = 4- MeO: **g**: R = 3,5-diMe



the reaction of the 2-indolylanion with a dipolarophile. This behaviour caused doubts about the effective intervention of an anionic species in the cycloaddition process. In fact, quenching the mixture resulting from prolonged refluxing of a solution of *N*-methylindole and ethylmagnesium bromide with deuterium oxide did not afford significant incorporation of deuterium in any position of the indole nucleus. Overall, these results give evidence that the rate enhancement phenomena described before cannot be related to the intermediacy of an anionic indole species.

Different mechanistic possibilities were considered. One involves the selective interaction of the magnesium of the Grignard reagent (Lewis acid) with the electron-rich moiety of the dipole (Lewis base) to give a complex that is much more reactive than dipole itself. This hypothesis is inadequate, in our case, for several reasons: (*a*) as reported above, ethylmagnesium bromide does not form complexes with **5** and **9**, but instantaneously degrades them, even at very low temperature; (*b*) it is known that nitrile oxide–Lewis acid complexes are in general less reactive than free nitrile oxides and that the stronger the Lewis acid, the less reactive is the complex;[5] and (*c*) the nitrogen atom of the indole ring must be involved somehow, since the corresponding reactions of thianaphthene are unaffected by the presence of the Grignard reagent.

A more articulated hypothesis suggests that the metal atom would establish a double coordination with the nitrogen atom of *N*-methylindole and with the electron-rich moiety of the dipole, to give a transition state for cycloaddition in which both the reactants are held together in an entropically favoured arrangement. Even though such a chelation satisfactorily accounts for the rate enhancement and regio- and stereoselectivity increase observed in a few cycloaddition reactions of nitrile oxides with allyl alcohols,[6] we considered this hypothesis harder to apply to the present case: in contrast to the situation produced in allyl alcohol–nitrile oxide cycloaddition reactions, where a conformationally favoured two-5,5-membered ring chelation can be arranged, a rather strained 5,4-membered ring chelation should be involved in our case. Even though this picture cannot be rejected, we are inclined to accept as the determinant step for rate enhancement the *N*-methylindole–ethylmagnesium bromide complexation. This

should produce an adduct more reactive toward dipoles than *N*-methylindole itself.

This hypothesis is supported by the observation that *N*-methylpyrrole is completely unreactive towards nitrile oxide **5** at 0 °C, in diethyl ether solution, for weeks. Instead, a very fast reaction takes place in the presence of one equivalent of ethylmagnesium bromide affording the regioisomeric oximes **15** and **16**, which probably result from ring opening of unstable intermediate cycloadducts. Instead, thiophene was found unreactive under the same experimental conditions.

A different reaction path was observed when *N*-methylindole and nitrile oxide **5** reacted in the presence of an equimolar amount of magnesium bromide in diethyl ether at 0 °C. Reaction was still very fast, but a complex mixture of products was formed, in which oxime **12**, but no the cycloaddition product **11**, was detected.

We tried to increase the interaction between the Grignard reagent and the *N*-methylindole by changing the solvent (tetrahydrofuran, benzene, hexane) and the organomagnesium compound (phenyl, naphthyl, hexadecyl) with no substantial change in kinetics and yields.

The nature of the postulated reactive complex between indole and ethylmagnesium bromide was investigated through theoretical calculations, reported in the following section.

Theoretical investigation

X-ray structural information on the known complexes of organomagnesium compounds,[7–12] with magnesium coordinated to aminic-type nitrogen atoms, was taken as the starting point for modelling the *N*-methylindole–ethylmagnesium bromide complex. In fact, the coordination process is believed to involve a marked pyramidalization of the *N*-methylindole nitrogen atom, with a corresponding partial loss of aromaticity. The typical ranges for the values of bond lengths and angles in the six Grignard complexes indicate a deformed tetrahedral arrangement around magnesium, with smaller N—Mg—N angles and values of the other angles depending on the particular ligand skeleton; the Mg—N bond length lies between 2.13 and 2.35 Å.

The x-ray structure of the monomer unit EtMgBr-$(Et_2O)_2$ in the solid state[13] was assumed as a model for the Grignard reagent in diethyl ether solution, before coordination with the *N*-methylindole. In this structure the ethyl group, the bromine atom and the two ether groups are tetrahedrally arranged around the magnesium atom; the Mg—O distances are about 2.0 Å.

Reference electron distributions for the Grignard reagent with oxygen and nitrogen coordinated atoms were obtained from quantum mechanical calculations on $EtMgBr(Et_2O)_2$ and EtMgBr[(−)-α-isosparteine] (**17**) using their x-ray geometries.[10,13]

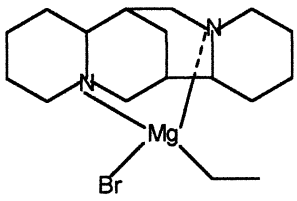


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Table 1 reports atomic charges obtained for these complexes using different population analysis schemes (see Computational methods section). The results refer to the 6–31G* + SV4P (for bromine) basis set. Atomic charges obtained within the framework of quantum theory of atoms in molecules (QTAM charges, Table 1) give a picture of the electron distribution of both the complexes which is the closest to chemical intuition; in contrast to the other investigated schemes, the most polarized bonds are those between the Lewis acid (organomagnesium) and the Lewis bases (ethers or sparteine). The expected strong polarization of Mg—Br and Mg—C bonds is confirmed and the charge of magnesium amounts to 1.7.

It is worth noting that the electronic distributions of the two complexes are alike, suggesting that the coordination with the ether or the amine molecules influences the organomagnesium compound in a similar way.

To verify the effects of varying the basis set in the electron distribution calculations, several basis sets were tested (see Computational methods section). The results, reported in Table 2 for the EtMgBr molecule, indicate that the atomic charges change significantly on extending the basis set from the 3–21G* to the 6–31G* and SV4P (for bromine). In contrast, the further improvement to the (14s11p5d)(d) basis set for bromine causes only very slight variations in the charge values of bromine and magnesium atoms. Therefore, all calculations on EtMgBr complexes were performed with the 6–31G* + SV4P basis set.

The structure of the hypothesized Grignard–*N*-methylindole complex was modelled from $EtMgBr(Et_2O)_2$, but with only one ether molecule, and *N*-methylindole coordinated at the nitrogen atom. The initial Mg—N distance was assumed to be the largest one in the nitrogen complexes investigated (2.35 Å). The whole structure of the EtMgBr(*N*-methylindole)(Et_2O) complex was then fully optimized with the 3–21G* basis set. It has been demonstrated[8] that this basis provides a satisfactory description of equilibrium geometries for many halogenated compounds. As a check, we calculated the 3–21G* equilibrium geometry for the $EtMgBr(Et_2O)_2$ complex. The results are in excellent agreement with the x-ray experimental structure; the magnesium tetrahedral environment is completely reproduced and only the torsional angles of ethylic chains are slightly different.

The optimized structure of EtMgBr(*N*-methylindole)(Et_2O) is depicted in Fig. 1. The steric hindrance of *N*-

Table 1. Atomic charges for $EtMgBr(Et_2O)_2$ and EtMgBr[(−)-α-isosparteine] obtained by different population analysis schemes (see text) with the 6–31G* + SV4P basis set

Complex	Atom	Mulliken charge	Natural population charge	QTAM charge
$EtMgBr(Et_2O)_2$	Mg	+0.944	+1.636	+1.729
	O_1	−0.763	−0.769	−1.322
	O_2	−0.734	−0.755	−1.356
	Br	−0.622	−0.869	−0.888
	C	−0.651	−1.125	−0.537
EtMgBr[(−)-α-isosparteine]	Mg	+0.842	+1.649	+1.711
	N_1	−0.780	−0.694	−1.426
	N_2	−0.785	−0.702	−1.366
	Br	−0.613	−0.859	−0.885
	C	−0.644	−1.132	−0.507

methylindole causes the indole ring and the diethyl ether group to assume an opposite mutual orientation. In addition, one of the ethyl chains in diethyl ether modifies the C—C—O—Mg torsion angle of about 30° with respect to $EtMgBr(Et_2O)_2$ and the indole aromatic ring turns out to be nearly perpendicular to the Mg—N bond.

Comparison of the most significant bond lengths and angles of this complex with those of $EtMgBr(Et_2O)_2$, shown in Table 3, reveals that the tetrahedral arrangement around magnesium is still deformed to smaller ligand—Mg—ligand and larger Br—Mg—C angles. As regards bond lengths, only the C—C bond in the ethylic fragment is significantly longer than that in the reference compound, the others remaining virtually unchanged. The Mg—N bond length is similar to that of the model complex **17** (Table 3) and represents the average value for the known Grignard complexes containing nitrogen atoms.

On the basis of these observations, it appears that the arrangement of atoms around magnesium and the strength of the coordination bonds with both the oxygen and nitrogen atoms are those typically found in Grignard complexes. Accordingly, the QTAM charges of EtMgBr(*N*-methylindole)(Et_2O), in Table 4, resemble those obtained with the same method for the model complexes (Table 1); the greater negative charge on the nitrogen atom (−1.589 vs −1.426 or −1.366 in the model complexes) is related only to the different kind of hybridization and molecular environment of this atom with respect to the reference aminic nitrogens. The atomic charge on the nitrogen in the isolated *N*-methylindole amounts to −1.642, to be compared with −1.171 for methylamine.

All these points confirm that *N*-methylindole and ethylmagnesium bromide in diethyl ether solution can form an adduct with the same characteristics as the known stable Grignard complexes. Let us analyse the effects of coordination on *N*-methylindole. A PMO analysis of the molecular orbitals and their energies should help in explaining the observed change in reactivity. Indeed, a simple FMO analysis may explain the different reactivity of the coordinate *N*-methylindole towards nitrilimines produced from halohydrazones **9a**–**d** with respect to those from **9e**–**g**. The comparison of the HOMO–LUMO energy gaps indicates dipole–LUMO control for all these reaction, suggesting the electron-donor groups on the dipoles reduce reactivity. Moreover, the observed regioselectivities cannot be related to the small difference in the size of terminal HOMO coefficients of the dipolarophile, but they can be explained on the basis of the stabilizing coulombic interactions between the electron-rich C_2 atom of *N*-methylindole and the electron-poor carbon atom in nitrile oxide or nitrilimine and between the C_1 and the oxygen or nitrogen atom on dipoles. As in most 1,3-dipolar cycloaddition reactions where compounds with high local charge densities are involved, the electrostatic interactions play a more important role than the stabilizing interaction between filled and vacant orbitals in determining regioselectivity.

However, it is worth noting that all these characteristics are very similar in the isolated and the coordinated *N*-methylindole, *i.e.* they are only slightly influenced by coordination with the Grignard reagent. On the other hand, the MO stabilization observed in the *N*-methylindole complex with respect to the isolated molecule, a

Table 2. QTAM atomic charges of EtMgBr obtained with different basis sets

	Basis set (number of basis functions)		
Atom or group	3–21G* (76)	6–31G* + SV4P (88)	6–31G* + (14s11p5d)(d) (142)
Mg	1.717	1.658	1.660
Br	−0.896	−0.881	−0.883
C_1	−0.706	−0.660	−0.660
C_2	−0.027	0.081	0.081
Et^-	−0.821	−0.777	−0.777

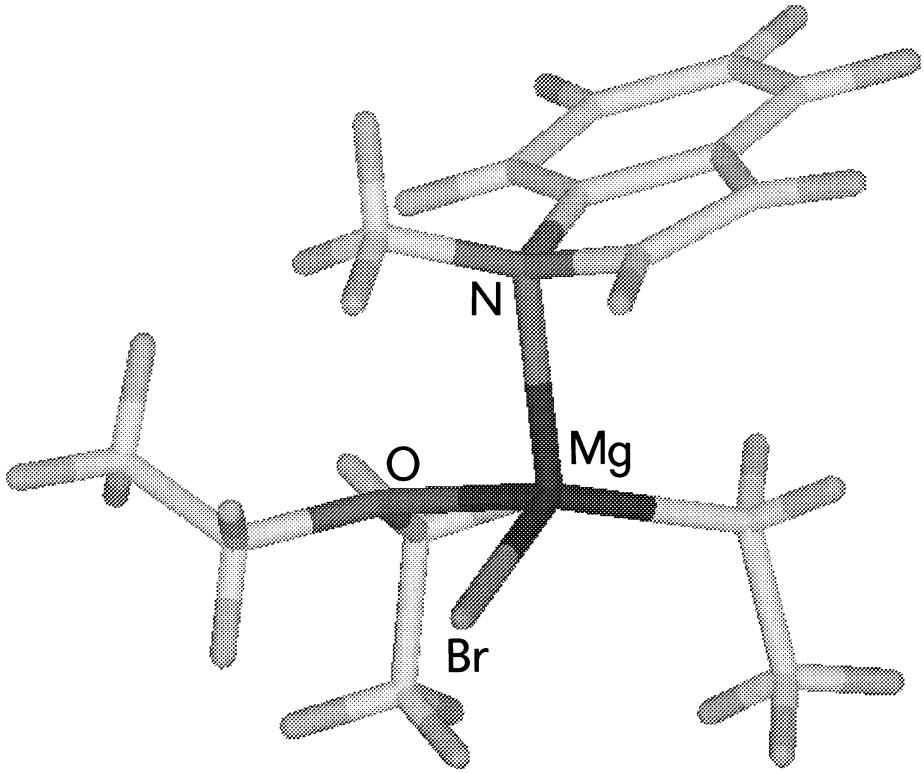


Figure 1. The 3–21G* optimized structure of EtMgBr(*N*-methylindole)(Et_2O)

consequence of coordination with the Lewis acid, cannot explain the Grignard reagent-induced rate enhancement.

A careful analysis of the effects of coordination on the structure and the electronic distribution of *N*-methylindole sheds light on this matter. The 3–21G* optimized structures of the *N*-methylindole moiety in the modelled complex and in the isolated molecule are reported in Table 5. The benzene ring characteristics are similar in the two structures, whereas the five-membered ring is strongly affected by coordination. In fact, the dihedral angles indicate the planarity of the whole skeleton in the isolated *N*-methylindole and a slight deformation from planarity of the five-membered ring, accompanied by a strong modification of the dihedral angle involving the

Table 3. 3–21G* optimized structure of EtMgBr(*N*-methylindole)(Et_2O) compared with the x-ray geometries of EtMgBr$(Et_2O)_2$ and EtMgBr[(−)-α-isosparteine)]

Complex	Bond length	(Å)	Bond angle	(°)
EtMgBr(*N*-methylindole)(Et_2O)	Mg—N	2.234	N—Mg—O	97.1
	Mg—O	2.044	Br—Mg—O	103.2
	Mg—Br	2.428	Br—Mg—N	100.8
	Mg—C	2.148	C—Mg—O	111.2
	C—C	1.558	C—Mg—N	109.5
			Br—Mg—C	129.9
EtMgBr$(Et_2O)_2$	Mg—O_1	2.027	O_1—Mg—O_2	101.2
	Mg—O_2	2.053	Br—Mg—O_1	102.9
	Mg—Br	2.476	Br—Mg—O_2	103.7
	Mg—C	2.148	C—Mg—O_1	111.7
	C—C	1.452	C—Mg—O_2	109.6
			Br—Mg—C	125.0
EtMgBr[(−)-α-isosparteine]	Mg—N_1	2.163	N_1—Mg—N_2	83.9
	Mg—N_2	2.195	Br—Mg—N_1	122.9
	Mg—Br	2.506	Br—Mg—N_2	101.4
	Mg—C	2.240	C—Mg—$N_1$106.1	
	C—C	1.390	C—Mg—N_2	129.7
			Br—Mg—C	112.1

Table 4. QTAM charges for EtMgBr(*N*-methylindole(Et_2O) calculated with the 6–31G* + SV4P basis set

Atom	QTAM charge
Mg	+1.720
N	−1.589
O	−1.325
Br	−0.886
C	−0.565

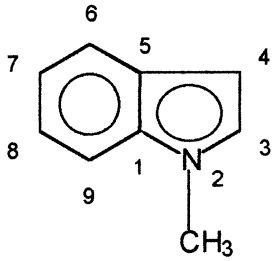
methyl group (C_{10}—C_2—C_3—C_4), in the coordinated form. The bond angles confirm the change in the nitrogen hybridization from sp^2 towards a nearly tetrahedral arrangement. In the coordinated form, the N_2—C_3 and C_4—C_5 bond lengths are found to be significantly longer and the C_3—C_4 shorter than in the isolated case.

Table 6 lists a number of bond critical point (BCP) properties for selected bonds in the isolated and coordinated *N*-methylindole. The reported properties include the density ρ_b and the density curvature along the bond path λ_3. At BCP two curvatures (λ_1 and λ_2) are negative and are associated with eigenvectors which define an interatomic surface orthogonal to the bond path at the BCP, whereas the positive curvature λ_3 is associated with an eigenvector defining the bond path at the BCP. Also reported are the bond order *n* and the bond ellipticity ε [$\varepsilon = (\lambda_1/\lambda_2) - 1$], which, being a measure of the extent to which charge preferentially accumulates in a given plane, relates to the π bond character. Table 6 shows that the changes induced by coordination of *N*-methylindole in the bond order *n* of the five-membered ring agree with the observed geometrical changes. The C_3—C_4 bond order increases from 1.87 to 2.02, a value close to that of ethylene (2.1). Conversely, the C—N bonds in the ring have their bond order slightly decreased. The C_4—C_5 bond undergoes a small decrease in its bond order but a significant lowering of its ellipticity. The latter fact, along with the halving of C—N bond ellipticities in the ring, confirms that the complex formation causes an enhancement of the enaminic character of the N_2—C_3—C_4 fragment, accompanied by a partial isolation of the C_3—C_4 double bond from the π-conjugated framework.

CONCLUSIONS

The most interesting result found in the cycloaddition experiments of nitrilimines and nitrile oxides with *N*-methylindole in the presence of a Grignard reagent is a very high and unexpected rate enhancement. Under these conditions the reaction is complete in seconds at 0 °C, whereas it is reported generally to require days or weeks at room temperature. Cycloaddition products are immediately formed, although in modest yields, under reaction conditions in which both of these dipoles are found to be highly unstable. Instead, thianaphthene is totally unreactive. We suggest that the rate enhancement observed could be related to the formation of an adduct

Table 5. 3–21G* optimized structures of the *N*-methylindole moiety in the EtMgBr(*N*-methylindole) (Et_2O) complex and in the isolated molecule (in parentheses)



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Bond length (Å)			Bond angle (°)			Dihedral angle (°)		
1–2	1.372	(1.372)	1–2–3	105.4	(108.1)			
2–3	1.440	(1.373)	2–3–4	110.6	(110.8)	2–3–4–5	2.4	(0.0)
3–4	1.336	(1.348)	3–4–5	108.0	(106.5)	3–4–5–6	−178.6	(−180.0)
4–5	1.459	(1.440)	4–5–1	107.1	(106.5)	4–5–6–7	179.5	(180.0)
5–6	1.387	(1.398)	1–5–6	119.8	(119.2)	5–6–7–8	−0.2	(−0.0)
6–7	1.380	(1.375)	5–6–7	118.6	(119.1)	6–7–8–9	−0.3	(0.0)
7–8	1.394	(1.403)	6–7–8	120.9	(120.8)	7–8–9–1	0.3	(0.0)
8–9	1.381	(1.376)	7–8–9	121.1	(121.3)	8–9–1–5	0.2	(0.0)
1–9	1.382	(1.395)	8–9–1	117.6	(117.6)	1–2–3–4	−4.2	(−0.0)
1–5	1.392	(1.402)	9–1–5	122.0	(122.0)	10–2–3–4	−139.9	(−180.0)
2–10	1.395	(1.440)	5–1–2	108.7	(108.1)	5–1–2–3	4.3	(0.0)
			10–2–3	117.9	(126.2)	4–5–1–2	−3.0	(0.0)

Table 6. RHF/6–31G*//3–21G bond critical point properties for selected bonds in coordinated and isolated (in parentheses) *N*-methylindole

Bond	b	λ_3	ε	*n*
3–4	0.358	0.20	0.45	2.02
	(0.346)	(0.20)	(0.44)	(1.87)
4–5	0.286	0.30	0.11	1.29
	(0.291)	(0.29)	(0.16)	(1.33)
2–3	0.278	0.33	0.03	1.25
	(0.300)	(0.66)	(0.09)	(1.37)
1–2	0.286	0.33	0.02	1.29
	(0.309)	(0.69)	(0.07)	(1.43)
1–5	0.331	0.27	0.24	1.71
	(0.324)	(0.28)	(0.23)	(1.63)
Ethane	0.245	0.29	0.00	1.00
Ethylene	0.364	0.19	0.45	2.10
Methylamine	0.265	0.18	0.03	1.00
Methyleneimine	0.399	1.44	0.26	1.86

between the dipolarophile (a Lewis base) and the organomagnesium compound (a Lewis acid), involving the aromatic nitrogen and the magnesium atom. Theoretical modelling indicates that structural and electronic characteristics of the adduct are the same of known Grignard complexes. Moreover, the dipolarophilic character and the reactivity of the *N*-methylindole double bond, involved in the 1,3-dipolar cycloaddition mechanism, increase as a result of coordination with ethylmagnesium bromide.

COMPUTATIONAL METHODS

Electron distributions were obtained from *ab initio* HF-SCF wavefunctions. A number of different Gaussian basis sets were analysed, namely a minimal basis set (STO-3G),[14] two standard split-valence basis sets, 3–21G* and 6–31G*, for first- and second-row atoms[14] and *ad hoc* bases, specifically developed for third- and fourth-row atoms, for bromine. These latter are the split-valence 3–21G basis developed by Dobbs and Hehre[15] augmented by *d*-type polarization functions, the SV4P basis set,[16] which is a split-valence plus polarization basis set obtained from a (43321/4321/4) contraction of the Huzinaga (4333/433/4) basis set,[17] originally developed for the halogens, and the large uncontracted (14s11p5d)(d) Dunning basis set,[18] with *d*-type polarization functions.

Molecular geometries of the reference Grignard complexes were taken from crystallographic data; for *N*-methylindole and the *N*-methylindole–ethylmagnesium bromide complex the fully optimized 3–21G* geometry was used.

The Gaussian 92[19] package of programs was employed for all wavefunction calculation and for the atomic charge evaluations with either the conventional Mulliken analysis[20] or the 'natural population' procedure.[21] Atomic populations were also obtained in the framework of the quantum theory of atoms in molecules (QTAM),[22] by integrating the electron density over the atomic basins.

Within QTAM, the charge density ρ_b at the bond critical point (BCP) serves as a measure of the corresponding bond order.[22] In the case of C—X bonds (X = C, N), the bond orders *n* were computed according to the following relationship:

$$n = \exp[a\ (\rho_b - b)]$$

proposed by Bader *et al.*[23] In this expression ρ_b is the value of ρ at the C—X BCPs, while *b* is set to be equal to $_b$ (au) for the C—X reference single bond and *a* is determined by a least-squares method. The *a* and *b* parameters are functions of the C—X pair, the basis set adopted and the reference geometry used. By employing RHF/6–31G* // 3–21G densities for ethane, ethylene, acetylene (C—C bond calibration) and the same kind of densities for methylamine, methyleneimmine and hydrogen cyanide (C—N bond calibration), we obtained $a = 6.242$, $b = 0.245$ for C—C bonds and $a = 4.497$, $b = 0.229$ for C—N bonds.

QTAM calculations were performed with the PROAIMV package.[24]

EXPERIMENTAL

*Reaction of 2-benzo[*b*]thienyllithium with nitrile oxide* ***5***. A 1.6 M solution of butyllithium (1.96 mmol) in hexane was dropped into a solution of benzo[*b*]thiophene (1.83 mmol) in diethyl ether (10 cm^3) under nitrogen at 25 °C. The mixture was refluxed under stirring for 1 h, then chilled to 0 °C and the nitrile oxide **5** (1.9 mmol) was added. After stirring for 10 min water was added and the mixture was exhaustively extracted with diethyl ether. The combined organic layers were dried and evaporated to dryness. Chromatography of the residue on silica gel, with a light petroleum–diethyl ether (9:1) mixture as eluent, yielded the 3,5-dichloro-2,4,6-trimethylphenyl 2-benzo[*b*]thienyl ketoxime (**6**) (0.37 g, 56%), m.p. 186 °C (Found: C, 59.02; H, 4.13; N, 3.83. $C_{18}H_{15}Cl_2NOS$ requires C, 59.50; H, 4.16; N, 3.86%); ν_{max} (Nujol/cm^{-1}) 3100 (OH) and 1600 (C=C); δ_H (300 MHz; $CDCl_3$) 2.20 (6H, s, 2 and 6-Me), 2.60 (3H, s, 4-Me), 7.18 (1H, s, 3-H), 7.33–7.44 (2H, m, 5 and 6-H), 7.70 (1H, d, *J* 7.3, 4-H), 7.87 (1H, d, *J* 9.8, 7-H), 9.5 (1H, br s, OH); *m/z* 363 (M^+, 100%).

*Reaction of 3-benzo[*b*]thienyllithium with nitrile oxide* ***5***. A 1.6 M solution of butyllithium (2.3 mmol) in hexane was dropped into a solution of 3-bromobenzo[*b*]thiophene (2.3 mmol) in diethyl ether (10 cm^3) under nitrogen at −70 °C. After stirring for 30 min, nitrile oxide **5** (2 mmol) was added and the temperature was allowed to rise to 0 °C. The mixture was stirred for a

further 5 min, then quenched with water and exhaustively extracted with diethyl ether. The combined organic layers were dried and evaporated to dryness. Chromatography of the residue on silica gel, with a light petroleum–diethyl ether (8:2) mixture as eluent, yielded the 3,5-dichloro-2,4,6-trimethylphenyl 3-benzo[*b*]thienyl ketoxime (**7a**) (390 mg, 53%), m.p. 165 °C (Found: C, 59.30; H, 4.10; N, 3.89. $C_{18}H_{15}Cl_2NOS$ requires C, 59.50; H, 4.16; N, 3.86%); ν_{max} (Nujol/cm^{-1}) 3250 (OH); δ_H (300 MHz; $CDCl_3$) 2.28 (6H, s, 2 and 6-Me), 2.55 (3H, s, 4-Me), 7.36 (2H, m, 5 and 6-H), 7.67 (1H, m, 4-H) 7.72 (1H, m, 7-H), 8.12 (1H, br s, OH); *m/z* 363 (M^+, 100%). Further elution gave the 3,5-dichloro-2,4,6-trimethylphenyl 3-benzo-[*b*]thienyl ketoxime (**7b**) (50 mg, 7%), m.p. 124 °C (Found: C, 60.10; H, 4.20; N, 3.84. $C_{18}H_{15}Cl_2NSO$ requires C, 59.50; H, 4.16; N, 3.86%); ν_{max} (Nujol/cm^{-1}) 3150 (OH); δ_H (300 MHz; $CDCl_3$) 2.30 (6H, s, 2 and 6-Me), 2.50 (3H, s, 4-Me), 7.37 (2H, m, 5 and 6-H), 7.68 (1H, m, 4-H), 7.70 (1H, s, 2-H), 7.85 (1H, m, 7-H); *m/z* 363 (M^+, 100%).

*Reaction of 2-(*N*-methyl)indolyllithium with nitrile oxide **5**.* A 1.6 M solution of butyllithium (2.8 mmol) in hexane was dropped into a solution of *N*-methylindole (1.9 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2 mmol) in diethyl ether (10 cm^3) under nitrogen at 25 °C. After 1 h of refluxing, the mixture was chilled to −30 °C and the nitrile oxide **5** (2 mmol) was added. The mixture was stirred for 30 min, then quenched with water and extracted with diethyl ether. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with dichlomethane as eluent, yielded the 3,5-dichloro-2,4,6-trimethylphenyl 2-(*N*-methyl)indolyl ketoxime (**8**), which was crystallized from hexane (200 mg, 29%), m.p. 141 °C (Found: C, 63.80; H, 5.35; N, 7.74. $C_{19}H_{18}Cl_2N_2O$ requires C, 63.32; H, 5.04; N, 7.78%); ν_{max} (Nujol/cm^{-1}) 3200 (OH) and 1600 (C = C); δ_H (200 MHz; $CDCl_3$) 2.25 (6H, s, 2 and 6-Me), 2.50 (3H, s, 4-Me), 3.8 (3H, s, NMe), 6.45 (1H, s, 3-H), 7.12 (1H, t, *J* 5, 5-H), 7.24 (1H, m, 6-H), 7.35 (1H,d,*J* 5, 4-H), 7.65 (1H, d, *J* 5, 7-H); *m/z* 343 (M^+, 100%) and 360 ($M^+ + 17$).

*Reaction of 2-(*N*-methyl)indolyllithium with ethyl 2-chloro-2-(4-chloro)phenylhydrazonoacetate.* A 1.6 M solution of butyllithium (3.0 mmol) in hexane was dropped into a solution of *N*-methylindole (2.3 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2.7 mmol) in diethyl ether (10 cm^3) under nitrogen at 25 °C. The mixture was refluxed under stirring for 1 h, then chilled to 0 °C and a solution of ethyl 2-chloro-2-(4-chloro)-phenylhydrazoneacetate (1.1 mmol) in diethyl ether was added. The reaction mixture was stirred for 1 h, poured into water and extracted with diethyl ether. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with dichloromethane as eluent, yielded the ethyl 2-[*N*-methylindolyl]-2-(4-chloro)phenylhydrazonoacetate (**10**) (39 mg, 10%) (Found: C, 63.84; H, 5.33; N, 11.80. $C_{19}H_{18}ClN_3O_2$ requires C, 64.21; H, 5.11; N, 11.83%); δ_H (200 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7, CH_3CH_2), 3.95 (3H, s, NMe), 4.42 (2H, q, *J* 7, CH_3CH_2), 6.34 (1H, s, 3-H), 7.00–7.40 (7H, m, aromatics), 7.55 (1H, d, *J* 6, 7-H), 8.15 (1H, br s, NH); *m/z* 343 (M^+, 100%).

Reaction of N*-methylindole with nitrile oxide **5** in the presence of ethylmagnesium bromide.* A solution of *N*-methylindole (4 mmol) and ethylmagnesium bromide (4.2 mmol, 3 M solution in diethyl ether) in diethyl ether (25 cm^3) was refluxed for 1 h, then chilled to 0 °C and a solution of nitrile oxide **5** (4 mmol) in diethyl ether (120 cm^3) was added. The mixture was stirred for 15 min and then poured into water and extracted with diethyl ether. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with a dichloromethane–hexane (1:1) mixture as eluent, yielded the 3-(3,5-dichloro-2,4,6-trimethylphenyl)-3a,8a-diidro-(8-methyl)indolo[2,3-*d*]isoxazole (**11**) (202 mg, 14%) (Found: C, 63.32; H, 5.13; N, 7.61. $C_{19}H_{18}O_2ClN_3$ requires C, 63.17; H, 5.02; N, 7.79%); δ_H (300 MHz; $CDCl_3$) 1.50 (3H, s, Me), 2.30 (3H,s, Me), 2.55 (3H, s, Me), 3.10 (3H, s, NMe), 4.90 (1H, d, *J* 8.3, 3a-H), 6.30 (1H, d, *J* 8.3, 8a-H), 6.49 (2H, d, *J* 7, 5 and 8-H), 6.55 (1H, t, *J* 7, 7-H), 7.1 (1H, t, *J* 7, 6-H); *m/z* 360 (M^+, 100%). Further elution gave 3,5-dichloro-2,4,6-trimethylphenyl 3-(*N*-methyl)indolyl ketoxime (**12**) (72 mg, 5%), m.p. 137 °C (Found: C, 63.27; H, 5.09; N, 7.74. $C_{19}H_{18}O_2ClN_3$ requires C, 63.17; H, 5.02; N, 7.79%); ν_{max} (Nujol/cm^{-1}) 3239 (OH), 1614 (C=C); δ_H (300 MHz; DMSO) 2.15 (6H, s, Me), 2.55 (3H, s, Me), 3.70 (3H, s, NMe), 6.90 (1H, s, 2-H), 7.2 (1H, t, *J* 7, 5-H), 7.25 (1H, t, *J* 7, 6-H), 7.45 (1H, d, *J* 7, 4-H), 8.18 (1H, d, *J* 7, 7-H), 10.75 (1H, s, OH); *m/z* 360 (M^+, 100%), 343 ($M^+ - 17$).

Reaction of N*-methylindole with ethyl 2-chloro-2-phenylhydrazonoacetate (**9a**) in the presence of ethylmagnesium bromide.* A solution of *N*-methylindole (18 mmol) and ethylmagnesium bromide (19 mmol, 3 M solution in diethyl ether) in tetrahydrofuran (25 cm^3) was refluxed for 40 min, then chilled to 0 °C and a solution of ethyl 2-chloro-2-phenylhydrazonoacetate (9 mmol) in tetrahydrofuran (15 cm^3) was added. The mixture was stirred for 1 h, then poured into cold water and extracted with diethyl ether. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with dichloromethane as eluent, yielded the 3a,8a-dihydro-3-ethoxycarbonyl-8-methyl-1-phenyl-pyrazolo[3,4-*b*]indole (**13a**), which was treated with propan-2-ol (230 mg, 8.5%) (Found: C, 71.23; H, 6.01; N, 13.15. $C_{19}H_{19}N_3O_2$ requires C, 71.01; H, 5.96; N, 13.07%); δ_H (300 MHz; $CDCl_3$) 1.38 (3H, t, *J* 8.5, CH_3CH_2), 2.96 (3H, s, NMe), 4.35 (2H, q, *J* 8.5, CH_3CH_2), 5.15 (1H, d, *J* 10, 3a-H), 6.21 (1H, d, *J* 10, 8a-H), 6.45 (1H, d, *J* 8, 8-H), 6.75 (1H, t, *J* 7, 7-H), 7.05 (1H,

t, *J* 5.6, 6-H), 7.15–7.45 (5H, m, Ph), 7.58 (1H, d, *J* 8, 5-H); *m/z* 321 (M^+, 100%).

Reaction of N*-methylindole with ethyl 2-chloro-2-(4-nitro)phenylhydrazonoacetate (**9c**) in the presence of ethylmagnesium bromide.* A solution of *N*-methylindole (18 mmol) and ethylmagnesium bromide (19 mmol, 3 M solution in diethyl ether) in tetrahydrofuran (25 cm^3) was refluxed for 40 min., then chilled to 0 °C and a solution of ethyl 2-chloro-2-(4-nitro)phenylhydrazonoacetate (**9c**) (9 mmol) in tetrahydrofuran (15 cm^3) was added. The mixture was stirred for 1 h, poured into water and extracted with dichloromethane. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with dichloromethane as eluent, yielded the 3a,8a-dihydro-3-ethoxycarbonyl-8-methyl-1-(4-nitro)phenylpyrazolo[3,4-*b*]indole (**13c**), which was crystallized from propan-2-ol (190 mg, 6%), m.p. 213 °C. (Found: C, 60.34; H, 5.30; N, 15.70. $C_{19}H_{18}N_4O_4$ requires C, 62.30; H, 4.92; N, 15.30%); ν_{max} (Nujol/ cm^{-1}) 1596 (C = C) and 1715 (C = O); δ_H (200 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.2, CH_3CH_2), 3.08 (3H, s, NMe), 4.37 (2H, q, *J* 7.2, CH_3CH_2), 5.22 (1H, d, *J* 10, 3a-H), 6.23 (1H, d, *J* 10, 8a-H), 6.52 (1H, d, *J* 8, 8-H), 6.78 (1H, t, *J* 8, 7-H), 7.17 (1H, t, *J* 8, 6-H), 7.44 (2H, d, *J* 8.8, aromatics), 7.48 (1H, d, *J* 8, 5-H), 8.21 (2H, d, *J* 8.8, aromatics); *m/z* 366 (M^+, 100%) and 292 ($M^+ - 74$).

Reaction of N*-methylindole with ethyl 2-chloro-2-(3-nitro)phenylhydrazonoacetate (**9d**) in the presence of ethylmagnesium bromide.* A solution of *N*-methylindole (18 mmol) and ethylmagnesium bromide (19 mmol, 3 M solution in diethyl ether) in tetrahydrofuran (25 cm^3) was refluxed for 40 min, then chilled to 0 °C and a solution of ethyl 2-chloro-2-(3-nitro)phenylhydrazonoacetate (**9d**) (9 mmol) in tetrahydrofuran (15 cm^3) was added. The reaction mixture was stirred for 2 h, poured into water and extracted with dichloromethane. The organic layer was dried and evaporated to dryness. Chromatography of the residue on silica gel, with a dichloromethane–hexane (9:1) mixture as eluent, yielded the 3a,8a-dihydro-3-ethoxycarbonyl-8-methyl-1-(3-nitro)phenylpyrazolo[3,4-*b*]indole (**13d**) (223 mg, 7%) (Found: C, 62.35; H, 4.98; N, 15.25. $C_{19}H_{18}N_4O_4$ requires C, 62.27; H, 4.95; N, 15.30%); δ_H (300 MHz; $CDCl_3$) 1.40 (3H, t, *J* 8.4, CH_3CH_2, 3.12 (3H, s, NMe), 4.40 (2H, q, *J* 8.4, CH_3CH_2), 5.20 (1H, d, *J* 10.3, 3a-H), 6.22 (1H, d, *J* 10.3, 8a-H), 6.53 (1H, d, *J* 8, 8-H), 6.80 (1H, t, *J* 8, 8-H), 7.18 (1H, t, *J* 8, 6-H), 7.50 (2H, t, *J* 8.9, 5-H), 7.75 (1H, dd, 4-H), 7.85 (1H, dd, 6-H), 8.15 (1H, d, 2-H); *m/z* 366 (M^+, 100%) and 292 ($M^+ - 74$).

Reaction of N*-methylindole with ethyl 2-chloro-2-(4-chloro)phenylhydrazonoacetate (**9b**) in the presence of ethylmagnesium bromide.* A solution of *N*-methylindole (18 mmol) and ethylmagnesium bromide (19 mmol, 3 M solution in diethyl ether) in tetrahydrofuran (25 cm^3) was refluxed for 40 min, than chilled to 0 °C and a solution of ethyl 2-chloro-2-(4-chloro)phenylhydrazonoacetate (9 mmol) in tetrahydrofuran (15 cm^3) was added. The reaction mixture was stirred for 1 h, then poured into water and the 3a,8a-dihydro-1-(4-chloro)phenyl-3-ethoxycarbonyl-8-methylpyrazolo[3,4-*b*]indole (**13b**) was recovered by filtration. It was triturated with ethanol (320 mg, 10%), m.p. 213 °C (Found: C, 64.33; H, 5.19; N 11.45. $C_{19}H_{18}ClN_3O_2$ requires C, 64.21; H, 5.11; N, 11.83%); ν_{max} (Nujol/ cm^{-1}) 1710 (C = O), 1600 (C = C); δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, CH_3CH_2), 2.95 (3H, s, NMe), 4.22 (2H, m, CH_3CH_2), 5.21 (1H, d, *J* 9.3, 3a-H), 6.51 (1H, d, *J* 9.3, 8a-H), 6.55 (1H, d, *J* 7.8, 8-H), 6.70 (1H, t, *J* 7.8, 8-H), 7.38 (1H, t, *J* 7.8, 5-H), 7.40 (4H, s, 4-ClC_6H_4); *m/z* 355 (M^+, 100%) and 281 ($M^+ - 74$).

*Reaction of nitrile oxide **5** with* N*-methylpyrrole in the presence of ethylmagnesium bromide.* A solution of *N*-methylpyrrole (3 mmol) and ethylmagnesium bromide (3.5 mmol, 3 M solution in diethyl ether) in benzene (30 cm^3) was refluxed for 30 min, then the solvent was removed until distillation temperature reached 79 °C. The suspension was chilled to 5 °C and a solution of nitrile oxide **5** (3 mmol) in benzene (15 cm^3) was added; the reaction mixture was stirred for 1 h, then poured into cold water and, after removal of benzene, it was extracted with dichloromethane. The organic layer was dried and evaporated to dryness. Chromatography on silica gel, with a dichloromethane–hexane (9:1) mixture as eluent, yielded a mixture of two products, which were separated by chromatography on silica gel with a dichloromethane–ethylacetate (9:1) mixture as eluent. The first product eluted was the 3,5-dichloro-2,4,6-trimethylphenyl 2-pyrrolyl ketoxime (**16**) (80 mg, 8.6%) (Found: C, 58.35; H, 5.10; N 9.21. $C_{15}H_{16}Cl_2N_2O$ requires C, 58.05; H, 5.20; N, 9.03%); δ_H (300 MHz; $CDCl_3$) 2.20 (6H, s, 10 and 13-Me), 2.50 (3H, s, 11-Me), 3.60 (3H, s, NMe), 6.30 (1H, d, 5-H), 6.35 (1H, d, 3-H), 6.55 (1H, m, 4-H); *m/z* 310 (M^+, 100%). The second product eluted was the 3,5-dichloro-2,4,6-trimethylphenyl 3-pyrrolyl ketoxime (**15**) (70 mg, 7.5%) (Found: C, 58.32; H, 5.19; N 9.15. $C_{15}H_{16}Cl_2N_2O$ requires C, 58.05; H, 5.20; N, 9.03%); δ_H (300 MHz; $CDCl_3$) 2.20 (6H, s, 10 and 13 Me), 2.50 (3H, s, 11-Me), 3.60 (3H, s, NMe), 6.00 (1H, t, 4-H), 6.50 (1H, t, 5-H), 7.35 (1H, s, 2-H), 8.5 (1H, br s, OH); m/z 310 (M^+, 100%).

Acknowledgements

The authors thank the CILEA computing center in Segrate for providing computational support and the Servizio Italiano di Diffusione dati Cristallografici of CNR (Parma) for access to the Cambridge Structural Database. Financial support by the Italian CNR

(CT94.01635.CT03 and CT95.01302.CT03) is gratefully acknowledged.

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