New Route to Nucleophilically Substituted *o*-Phenylenediamines

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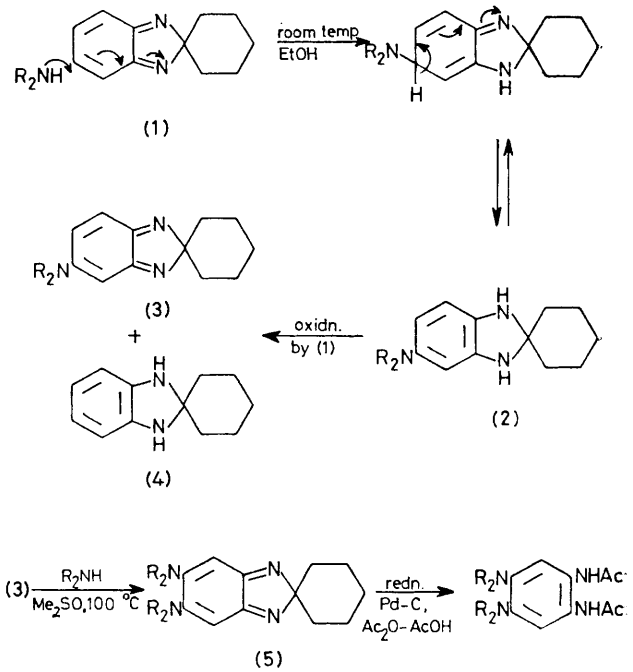
Summary 4-Dialkylamino- and 4,5-bis(dialkylamino)-*o*-phenylenediamines are conveniently prepared by treatment of isobenzimidazole-2-spirocyclohexane with secondary amines, followed by reductive hydrolysis; introduction of other nucleophiles by this method and examples of using these novel phenylenediamines in heterocyclic syntheses are also described.

o-PHENYLENEDIAMINES are versatile intermediates for the synthesis of a wide spectrum of heterocycles. Electrophiles can be directly introduced into *o*-phenylenediamines by nitration and halogenation or indirectly by protecting the *o*-diamine groups through a temporary formation of a heterocyclic intermediate such as a benzoselenodiazole[1] or benzothiadiazoles.[2] By contrast *o*-phenylenediamines with nucleophilic substituents, *e.g.* alkylamino-groups, are only available by cumbersome and multistep syntheses[3] which undoubtedly accounts for the sparse literature in this field.

We have now found that isobenzimidazole-2-spirocyclohexane (**1**), obtained in high yield[4] from *o*-phenylenediamine and cyclohexanone, will react with secondary amines in ethanol at ambient temperature to give an orange-red isobenzimidazole (**3**; *ca.* 40%) and in dimethyl sulphoxide or sulpholan at 100 °C to produce a yellow disubstituted isobenzimidazole (**5**; *ca.* 25%, Table 1) as shown in the Scheme.

The reaction is essentially a nucleophilic addition, followed by oxidation of the resultant substituted dihydrobenzimidazole (**2**) by an unchanged molecule of (**1**). 2,3-Dihydrobenzimidazole-2-spirocyclohexane (**4**) was isolated from the reaction mixtures in up to 50% yield. At higher temperature a further molecule of amine attacks (**3**), giving



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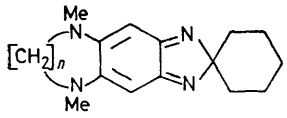
(**5**). However, compounds (**6**; $n = 2$ or 3, m.p. 190 or 140 °C, respectively) were prepared at room temperature. Addition of oxidising agents such as activated MnO_2 to the

reaction mixtures raised the yields of the mono-substituted compounds (**3**) only a little in most cases.

TABLE 1. Mono- and di-substituted isobenzimidazoles.

Compound	R_2	M.p./°C	Yield/%
(3a)	$-[CH_2]_4-$	177—178	43
(3b)	$-[CH_2]_5$	98—99	50
(3c)	$-[CH_2]_2O[CH_2]_2-$	100—103	41
(3d)	$-[CH_2]_2NMe[CH_2]_2-$	119—120	26
(3e)	$-[CH_2]_6-$	108—109	20
(5a)	$-[CH_2]_5-$	174	25
(5b)	$-[CH_2]_2O[CH_2]_2-$	220—222	20
(5c)	$-[CH_2]_2NMe[CH_2]_2-$	206—207	18

Primary amines gave lower yields of mono-substituted compounds; methylamine for instance furnished 22% of 5-(*N*-methylamino)isobenzimidazole-2-spirocyclohexane, m.p. 218—219 °C. Sulphur nucleophiles, such as benzenethiol, reacted vigorously with (**1**) at room temperature and gave the disubstituted product (**7a**). We have also prepared the mixed disubstituted isobenzimidazoles (**7b**) and (**7c**) from (**3b**) and others (Table 2). The thiazine (**7d**) was prepared by treating (**1**) with 2-aminoethanethiol hydrochloride using Na_2CO_3 as buffer. Reactions of (**1**) with some carbon nucleophiles have already been described.[5]



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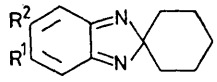

(7)

The substituted isobenzimidazoles [*e.g.* (**3**) or (**5**)] can be converted into the corresponding *NN'*-diacetylated *o*-phenylenediamines by reductive hydrolysis in Ac_2O–AcOH in presence of palladium–charcoal under hydrogen (Scheme) [*e.g.* (**3b**) gave 4-piperidino-*NN'*-diacetyl-*o*-phenylenediamine, m.p. 172—173 °C]. If the reduction is followed by addition of ethanolic hydrochloric acid and warming, (**3b**) yields 2-methyl-5-piperidino- (63%, m.p. 171—173 °C) and (**5a**) yields 2-methyl-5,6- dipiperidino-benzimidazole (83%, m.p. 279—281 °C). Similarly, addition of phenanthraquinone after the reduction gives 11-piperidino- (52%, m.p. 185—186 °C) and 11,12-dipiperidino-[*a*,*c*]phenazine (63%, m.p. 245 °C), respectively. Other examples of converting these novel phenylenediamines into various heterocycles by conventional routes will be published elsewhere. All new compounds gave correct analytical data.

TABLE 2. Some disubstituted isobenzimidazoles.

(7)	R^1	R^2	M.p./°C	Yield/%
a	PhS	PhS	201—203	27
b	4-Methylpyrazin-1-yl	Piperidino	180—181	38
c	PhS	Piperidino	166—167	71
d	$-S[CH_2]_2NH-$		173—174	35

Our method of introducing nucleophiles is thus complementary to the use of 2,1,3-benzoselenodiazoles for electrophilic substitution of phenylenediamines. The selenodiazole did not react with nucleophiles such as piperidine.

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