The Chemistry of *N*-Substituted Benzotriazoles. Part 4.[1] A Novel and Versatile Method for the Mono-*N*-alkylation of Aromatic and Heteroaromatic Amines

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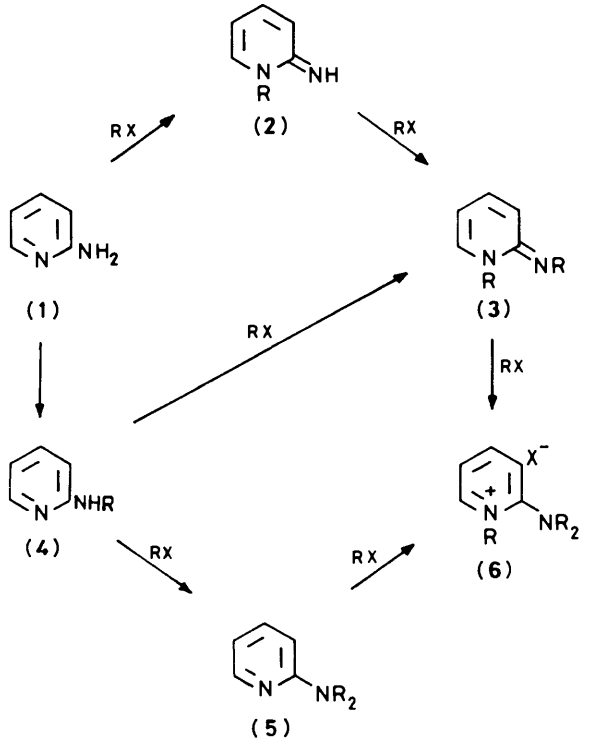
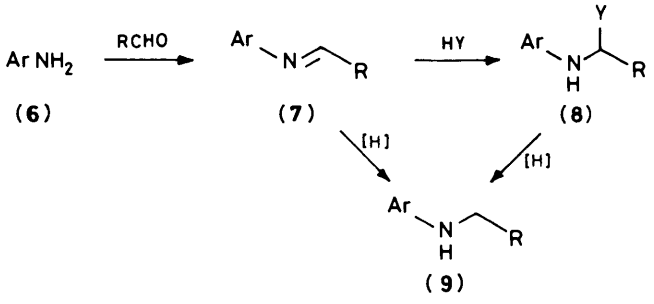
Mono-*N*-alkylation of aromatic and heteroaromatic amines is achieved in high yield by $NaBH_4$ reduction of the adducts formed from benzotriazole, aliphatic aldehydes and the amines. Reaction of the same adducts with Grignard reagents gives *N*-(secondary alkyl)arylamines. Carboxy groups need no protection and nitro groups are unaffected. Adenine is mono-*N*-alkylated in high yield.

N-Alkylarylamines ArNHR can be prepared by the direct alkylation of primary aromatic amines with alkyl halides,[2,3] alkyl sulphonates,[4] dialkyl phosphites,[5] or dimethyl oxalate,[6] provided a large excess of the starting amine is used. However, the separation of the product from the reaction mixture is difficult. Tertiary *N*,*N*-(dialkyl)arylamines are invariably by-products[7] because the *N*-alkylarylamines produced in the first step are more nucleophilic than the starting primary amines.[8–10] This problem intensifies if the aromatic ring bears electron withdrawing substituents. Alkylation of N-heterocyclic amines such as 2-aminopyridine (**1**),[11–15] can give two monoalkyl derivatives, (**2**) and (**4**) (Scheme 1); usually product (**2**) dominates strongly.[16–20] Therefore, direct alkylation is frequently unsatisfactory as a preparative method for the synthesis of alkylaminopyridines, alkylaminopyrimidines and other important alkylamino N-heterocycles.



Scheme 1.

One of the best solutions by the above problem of the monoalkylation of arylamines has been the use of aldehydes in a two-step sequence. Schiff bases (**7**) produced in the first step are then reduced to amines (**9**) (Scheme 2) using reducing agents such as sodium metal,[21] magnesium metal,[22] potassium graphite,[23] hydrogen in the presence of a nickel catalyst,[24] sodium borohydride,[25–30] lithium aluminium hydride,[31] Grignard reagents,[32] propan-2-ol in the presence of a rhodium catalyst,[33] silanes[34,35] or electrochemically.[36–38] Schiff bases derived from aromatic aldehydes can often be easily prepared and purified; after reduction they give benzylamino aromatics.[39] Schiff bases derived from aliphatic aldehydes are less stable and have usually been generated and reduced *in situ*.[39–41] A modification of this method is the use of alcohols as alkylating agents.[42–47] In the presence of Raney nickel, cobalt sulphide, an iridium triphenylphosphine complex or other catalysts, alcohols are dehydrogenated by the catalyst to aldehydes which give Schiff bases then reduced by the hydrogen produced.[42]



Scheme 2.

Considerable progress in the monoalkylation of primary amines came with the discovery that certain adducts of type (**8**) derived from Schiff bases can be used for the preparation of secondary amines. Often much more stable than the imines (**7**), compounds (**8**) can be isolated in high yield even when R is H or alkyl. Trapping (**7**) with HY to give (**8**) prevents many side reactions and increases the yield. Derivatives (**8**) with Y = alkoxyl[48] (limited to R = H), with Y = *p*-tolylthio,[49,50] and with Y = $SiHEt_2$ or other substitued silyl groups,[51] have previously been applied to give *N*-alkylarylamines (**9**), usually in good yield. Recently, Overman and Burk[51] have shown that cyano methylamines (**8**; R = H, Y = CN) react with RLi or RMgBr to give $RNHCH_2R^1$ in yields of 50—81%: they also treated 1-(anilinomethyl)benzotriazole with butyl-lithium and *N*-pentylaniline (59%).

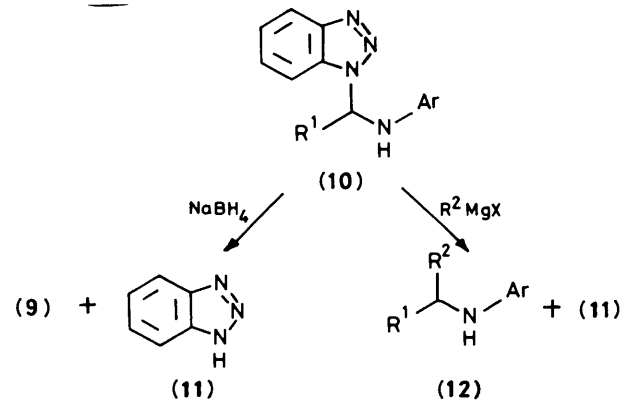
We now report that 1-(1′-arylaminoalkyl)benzotriazoles (**10**) [*i.e.* (**8**; Y = benzotriazol-1-yl)] derived from an aromatic amine, an aliphatic aldehyde, and benzotriazole,[1] are smoothly reduced to amines (**9**) by sodium borohydride or lithium aluminium hydride (Scheme 3). The procedure is simple and high yielding; no products from competing reactions were detected. Benzotriazole (**11**), which is produced along with (**9**) in the reaction, is easily separated by extraction with alkali and

Table 1. Comparison of the new method for the preparation of *N*-alkylarylamines with literature methods

	Starting Material (**10**)					Literature data		
Compd.	R^1	Ar	Reagent	Method	Yield (%)[a]	Starting materials	Yield (%)[b]	Ref.
(**13a**)	H	C_6H_4Cl-4	$LiAlH_4$	E	80	(a) 4-chloroaniline + $HC(OEt)_3$ (b) $NaBH_4$	66	55
(**13b**)	H	C_6H_4Cl-4	$PhCH_2MgCl$	F	85	4′-Chlorophenylacetanilide + $LiAlH_4$	not given	56
(**13c**)	H	$C_6H_4CO_2H$-4	$NaBH_4$	C	91	4-Aminobenzoic acid + formaldehyde + formic acid	40	81
(**13d**)	Pr	$C_6H_4CO_2H$-4	$NaBH_4$	C	85	(a) Ethyl *p*-aminobenzoate + butyl bromide + K_2CO_3 (b) NaOH	90	57
(**13e**)	H	$C_6H_4NO_2$-4	$NaBH_4$	C	89	4-Nitroaniline + trioxane	61	54
(**15a**)	H	2-Pyridyl	$LiAlH_4$	E	95	(a) 2-Aminopyridine + formaldehyde + 4-thiocresol (b) $NaBH_4$	67	49
(**15b**)	H	2-Pyridyl	$PhCH_2MgCl$	F	82	2-Bromopyridine + phenethylamine	48	60
(**16c**)	H	6-Methyl-2-pyridyl	CH_3MgI	F	76	6-Acetamido-2-methylpyridine + B_2H_6	33	82
(**17a**)	H	5-Chloro-2-pyridyl	$NaBH_4$	A	92	(a) 5-Chloropyridine-2-amine diethyl ethoxymethylenemalonate (b) methyl *p*-toluenesulphonate	not given	61
(**17d**)	H	5-Nitro-2-pyridyl	$NaBH_4$	C	89	2-Chloro-5-nitropyridine + methylamine	76	62
(**19a**)	H	Purin-6-yl	$NaBH_4$	D	75	1-Methyladenine (rearrangement)	65	83
(**19b**)	H	Purin-6-yl	PrMgI	G	71	(a) 6-mercaptopurine + dimethyl sulphate (b) butylamine	50	74
(**19c**)	H	Purin-6-yl	PhMgBr	G	80	Hypoxanthine + benzylamine + P_2O_5	40	75

[a] The yield is overall for both steps: aminoalkylation of benzotriazole and reduction or Grignard reaction. [b] When there are two steps for the preparation, the overall yield is given.

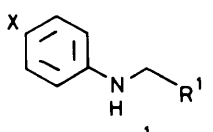
can be recovered in large-scale reactions. In this case, sodium borohydride, sodium carbonate, and hydrochloric acid are the only reagents used, apart from the starting amine and the aldehyde.



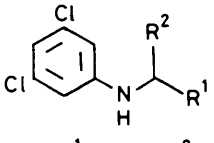
Scheme 3.

We further report that the benzotriazole moiety in (**10**) can readily be replaced by an alkyl group from a Grignard reagent leading to the amines (**12**). Such amines, with the nitrogen atom bonded to a secondary carbon atom, cannot be obtained by any of the methods of Scheme 2 mentioned above for the monoalkylation of aromatic amines. Hence, the two-step process now described for the monoalkylation of aromatic and heteroaromatic amines (**10**) is the most general available. The simplicity of the procedure, the wide variety of amines which can be alkylated, and yields usually better than those previously obtained (Table 1), are all attractive features.

The procedure has been applied to several substituted anilines. 4-Chloro-*N*-methylaniline (**13a**) was obtained by sodium borohydride reduction of 4-chloro-*N*-[(benzotriazol-1-yl)methyl]aniline (**10**; R^1 = H, Ar = C_6H_4Cl-*p*) in 80% yield (*cf.* literature methods which suggest 30—66%[52–55]). The same starting material (**10**) gave 4-chloro-*N*-phenethylaniline[56] (**13b**) on reaction with benzylmagnesium chloride. *N*-Alkylation of 4-aminobenzoic acid to give products (**13c**) and (**13d**) by sodium borohydride reduction of the appropriate (**10**; Ar = $C_6H_4CO_2H$-*p* and R^1 = H or Pr, respectively) was achieved without the protection of the carboxy group required in previous procedures.[57–59] Furthermore, the aromatic nitro group in amine (**10**; Ar = $C_6H_4NO_2$-*p*, R^1 = H) was unaffected by the reduction and work-up to (**13d**). *N*-Butylation of 3,5-dichloroaniline *via* reduction of the corresponding (**10**; R^1 = Pr, R^2 = $C_6H_3Cl_2$-3,5) smoothly afforded (**14a**). Reaction of the same (**10**) with methylmagnesium iodide led to previously unreported 3,5-dichloro-*N*-pentan-2-ylaniline (**14b**).



(**13**) **a**; X = Cl, R^1 = H
b; X = Cl, R^1 = CH_2Ph
c; X = CO_2H, R^1 = H
d; X = CO_2H, R^1 = Pr
e; X = NO_2, R^1 = H



(**14**) **a**; R^1 = Pr, R^2 = H
b; R^1 = Pr, R^2 = Me

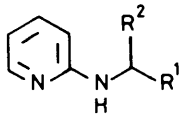
We have alkylated several heterocyclic amines. 2-Aminopyridine was first studied because of the complications in its alkylation mentioned above. As reported in the preceding paper,[1] 2-aminopyridine reacts with benzotriazole and aldehydes to give (**10**; Ar = 2-pyridyl) almost quantitatively. The

Table 2. Analytical data for new *N*-alkylarylamines

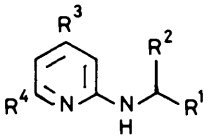
Product		Starting material							Found[a]			Required[a]		
No.	Formula	R^1	Ar	Reagent	Method	Yield (%)	Amine m.p. °C	Picrate m.p. °C	C	H	N	C	H	N
(**14a**)	$C_{10}H_{13}Cl_2N$	Pr	$C_6H_3Cl_2$-3,5	$NaBH_4$	A	68	Oil	—	*b*					
(**14b**)	$C_{11}H_{15}Cl_2N$	Pr	$C_6H_3Cl_2$-3,5	CH_3MgI	F	82	Oil	—	*c*					
(**15c**)	$C_9H_{14}N_2$	Pr^i	2-Pyridyl	$NaBH_4$	A	81	Oil	140—143	47.7	4.8	18.5	47.5	4.5	18.5
(**15d**)	$C_{10}H_{16}N_2$	Pr^i	2-Pyridyl	CH_3MgI	F	80	Oil	128—129	48.9	4.8	18.1	48.8	4.9	17.8
(**15e**)	$C_{10}H_{16}N_2$	Bu^t	2-Pyridyl	$NaBH_4$	A	96	67—68	—	72.8	10.2	16.8	73.1	9.8	17.1
(**15f**)	$C_{10}H_{14}N_2$	Me	2-Pyridyl	AllylMgBr		62	Oil	—	*c*					
(**6a**)	$C_7H_{10}N_2$	H	4-Methyl-2-pyridyl	$NaBH_4$	A	95	90—92	227—229	44.5	3.7	20.0	44.4	3.7	19.9
(**16b**)	$C_{14}H_{16}N_2$	H	4-Methyl-2-pyridyl	$PhCH_2MgCl$	F	78	Oil	198—200	54.4	4.3	15.6	54.4	4.3	15.9
(**16d**)	$C_8H_{12}N_2$	H	4,6-Dimethyl-2-pyridyl	$NaBH_4$	A	85	Oil	215—217	45.9	4.1	19.1	46.0	4.1	19.2
(**17b**)	$C_9H_{13}BrN_2$	Pr^i	5-Bromo-2-pyridyl	$NaBH_4$	A	98	45—47	168—169	39.4	3.4	15.3	39.3	3.5	15.3
(**18a**)	$C_8H_{13}N_3$	Pr	Pyrimidin-2-yl	$NaBH_4$	B	98	Oil	123—124	43.9	4.2	21.9	44.2	4.2	22.1
(**18b**)	$C_{12}H_{13}N_3$	C_6H_4Me-4	Pyrimidin-2-yl	$NaBH_4$	B	91	122—123	—	72.5	6.8	21.3	72.3	6.6	21.1
(**18c**)	$C_{15}H_{19}N_3$	Pr	Pyrimidin-2-yl	$PhCH_2MgCl$	F	95	Oil	168—170	53.9	4.8	17.7	53.6	4.7	17.9

[a] For the corresponding picrate, when a m.p. given for picrate. [b] Found: M^+, 217.0414. $C_{10}H_{13}Cl_2N$ requires *M*, 217.0425. [c] Found: M^+, 231.0566. $C_{11}H_{15}Cl_2N$ requires *M*, 231.0581. [d] Found: M^+, 162.1142. $C_{10}H_{14}N_2$ requires *M*, 162.1157.

reduction of 2-(benzotriazol-1-ylmethylamino)pyridine (**10**; Ar = 2-pyridyl, R^1 = H) gave smoothly 2-methylaminopyridine (**15a**) 95% (*cf.* the 67% reported previously[49]). The same starting material (**10**) with benzylmagnesium chloride afforded 2-phenethylaminopyridine[60] (**15b**). 2-[1-(Benzotriazol-1-yl)-2-methylpropylamino]pyridine (**10**; Ar = 2-pyridyl, R^1 = Pr^i) gave 2-isobutylaminopyridine (**15c**) on reduction with sodium borohydride and 2-(1,2-dimethylpropylamino)pyridine (**15d**) with methylmagnesium iodide. The presence of a bulky t-butyl group on the α-carbon in (**10**; Ar = 2-pyridyl, R^1 = Bu^t] did not affect the reduction leading to 2-(2,2-dimethylpropylamino)pyridine (**15e**) which was accomplished under the normal conditions. Reaction of (**10**) with allylmagnesium bromide gives *N*-alkenyl aromatic amines in which the terminal double bond is available for transformation into other useful functionalities. 2-[1-(Benzotriazol-1-yl)ethylamino]pyridine (**10**; Ar = 2-pyridyl, R^1 = methyl) thus afforded 2-(pent-1-en-4-yl-amino)pyridine (**15f**), 62%.

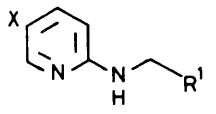


(**15**) **a**; $R^1 = R^2 = H$
b; $R^1 = CH_2Ph$, $R^2 = H$
c; $R^1 = Pr^i$, $R^2 = H$
d; $R^1 = Pr^i$, $R^2 = Me$
e; $R^1 = Bu^t$, $R^2 = H$
f; $R^1 = CH_2CH{=}CH_2$, $R^2 = Me$

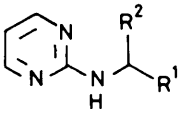


(**16**) **a**; $R^1 = R^2 = R^4 = H$, $R^3 = Me$
b; $R^1 = CH_2Ph$, $R^2 = R^4 = H$, $R^3 = Me$
c; $R^1 = R^4 = Me$, $R^2 = R^3 = H$
d; $R^1 = R^2 = H$, $R^3 = R^4 = Me$

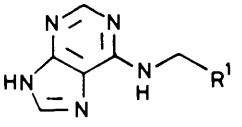
Alkylation of 2-amino-4-methylpyridine was also successfully accomplished *via* borohydride reduction of 2-[(benzotriazol-1-yl)methylamino]-4-methylpyridine (**10**; R^1 = H, Ar = 4-methyl-2-pyridyl) to 2-methylamino-4-methylpyridine (**16a**) or reaction with benzylmagnesium chloride to give 2-phenethylamino-4-methylpyridine (**16b**). Similarly, 6-ethylamino-2-methylpyridine (**16c**) was obtained by reduction of (**10**; R^1 = Me, Ar = 6-methyl-2-pyridyl). Borohydride reduction of 6-[(benzotriazol-1-yl)methylamino]-2,4-dimethylpyridine (**10**; R^1 = H, Ar = 4,6-dimethyl-2-pyridyl) gave 6-methylamino-2,4-dimethylpyridine (**16d**) (85%).



(**17**) **a**; R^1 = H, X = Cl
b; $R^1 = CH_2Ph$, X = Cl
c; $R^1 = Pr^i$, X = Br
d; R^1 = H, $X = NO_2$



(**18**) **a**; $R^1 = Pr$, $R^2 = H$
b; $R^1 = C_6H_4$-Me-4, $R^2 = H$
c; $R^1 = Pr$, $R^2 = CH_2Ph$



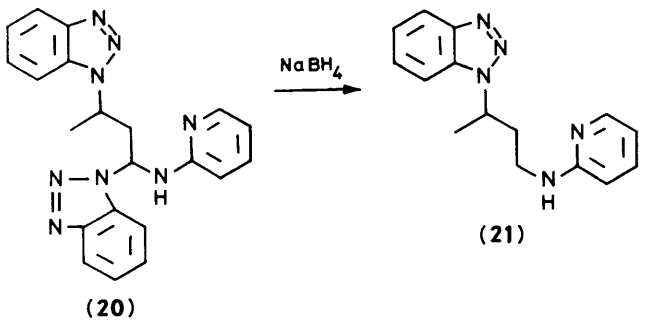
(**19**) **a**; $R^1 = H$
b; $R^1 = Pr$
c; $R^1 = Ph$

2-[(Benzotriazol-1-yl)methylamino]-5-chloropyridine (**10**; R^1 = H, Ar = 5-chloro-2-pyridyl) with sodium borohydride gave smoothly 2-methylamino-5-chloropyridine[61] (**17a**) and with benzylmagnesium chloride gave 2-phenethylamino-5-chloropyridine (**17b**). Reduction of 2-[1-(benzotriazol-1-yl)-2-methylpropylamino]-5-bromopyridine led to 2-isobutylamino-

5-bromopyridine (**17c**) (98%). As in the case of 4-nitroaniline, the nitro group in the 5-nitro-2-pyridyl substituent of (**10**; R^1 = H, Ar = 5-nitro-2-pyridyl) was unaffected under the standard conditions which gave 2-methylamino-5-nitropyridine[62] (**17d**) (89%). In this last case, the combined electron withdrawing effect of the nitro group and the pyridyl ring (*cf.* the pK_a of 15.8 of 2-amino-5-nitropyridine)[63] accelerate the reaction with sodium borohydride which required only 10 mins.

Similar activation of the benzotriazole bond was observed in compounds (**10**) derived from 2-aminopyrimidine. Thus, the reduction of 2-[(1-benzotriazol-1-yl)butylamino]pyrimidine (**10**; R^1 = Pr, Ar = pyrimidin-2-yl) to 2-butylaminopyrimidine (**18a**) and that of 2-[α-(benzotriazol-1-yl)-4-methylbenzylamino]pyrimidine (**10**; R^1 = 4-MeC_6H_4, Ar = pyrimidin-2-yl) to 2-(4-methylbenzylamino)pyrimidine (**18b**) was also fast. 2-(1-Phenyl-2-pentylamino)pyrimidine (**18c**) was obtained in 95% yield from (**10**; R^1 = Pr, Ar = pyrimidin-2-yl) by reaction with benzylmagnesium chloride.

The alkylation of adenine is of interest because of the potent biological activity of some of the products. Thus, 6-[(benzotriazol-1-yl)methylamino]purine (**10**; R^1 = H, Ar = 6-purinyl) gave 6-methylaminopurine (**19a**), which occurs in viral and bacterial DNA,[64–73] in 75% yield. Because of the low solubility of (**19a**) in organic solvents, continuous extraction into chloroform was used for its separation. Treatment of the same starting material (**10**) with propylmagnesium iodide afforded 6-butylaminopurine[74] (**19b**). The similar reaction with phenylmagnesium bromide led to 6-benzylaminopurine[75] (**19c**), a well known plant growth regulator.[76–80]



Scheme 4.

The reduction of 2-[1,3-di(benzotriazol-1-yl)butylamino]-pyridine (**20**) (Scheme 4), obtained from the reaction of benzotriazole with crotonaldehyde,[1] exemplifies the activation of the N–C bond attaching a benzotriazole 1-substituent by an α amino group. Product (**21**) was obtained with sodium borohydride under normal conditions, but further reduction of (**21**) was resisted. Treatment of (**21**) with methylmagnesium iodide, produced no reaction.

Experimental

For general methods and details of instrumentation, see Part 1 of this series.

Reduction of N-[1-(*Benzotriazol-1-yl*)*alkyl*]*arylamines* (**10**).—*General procedure* A. Compound (**10**) (10 mmol) and sodium borohydride (0.38 g, 10 mmol) was stirred and heated under reflux for 8 h with tetrahydrofuran (THF) (25 ml, distilled over sodium–benzophenone). When the starting amine (**10**) contained active hydrogen atoms (OH or NH groups), double the amount of sodium borohydride was used. The mixture was poured into ice–water (100 ml) and extracted with ether (2 × 50 ml). The ethereal layer was washed with 5% aqueous sodium carbonate (20 ml) and with water, dried ($MgSO_4$), and evaporated to afford the crude product of purity usually higher than 90% by ^1H n.m.r. Solids were recrystallized, and liquid amines characterized as their picrates.

General procedure B. Similar to procedure A, except that refluxing was for 20 min only.

General procedure C. As for procedure B, except that after pouring into ice–water, the whole was neutralized with 2% HCl and continuous extraction with chloroform–acetone (4:1) was carried out for 20 h. Chloroform was evaporated and the residue was dried *in vacuo* giving a mixture of the desired (**10**) and benzotriazole, which was triturated with THF (10 ml). The solid amine was separated and recystallized from ethanol.

General procedure D. As for procedure A but instead of THF, dry dioxane was used as the solvent. The reaction was carried out for 20 h under reflux. The work-up was analogous to that for procedure C.

Reduction of (**10**) *by lithium aluminium hydride: general procedure* E. To a stirred suspension of lithium aluminium hydride (0.38 g, 10 mmol) in dry THF (10 ml), kept under nitrogen, was added, dropwise, (**10**) (10 mmol) in THF (15 ml) during 30 min. The solution was stirred for an additional 30 min, poured into ice–water, neutralized with 2% HCl, and extracted with ether (2 × 50 ml). The ethereal solution was washed with water, with 5% aqueous sodium carbonate and again with water, and then dried ($MgSO_4$). Evaporation of the solvent afforded the crude *N*-allylarylamine with a purity similar to that obtained by applying procedure A.

Reaction of N-[(1-*benzotriazol*-1-*yl*)*alkyl*]*aminoarenes* (**10**) *with Grignard reagents: general procedure* F. To a Grignard reagent prepared from magnesium turnings (0.48 g, 20 mmol) and alkyl or aryl halide (15 mmol) in anhydrous diethyl ether, was added the appropriate (**10**) (10 mmol) over 15 min. The mixture was stirred at 25 °C for 16 h and then poured into ice–water. Further work-up as in procedure E.

Reaction of (**10**) *with Grignard reagents: general procedure* G. The reaction was carried out under conditions as in procedure F. Reaction work-up was according to procedure C.

Preparation of Picrates: General Procedure.—A saturated solution of picric acid in ethanol–water (1:1) was added dropwise to a 30% solution of amine in ethanol until formation of a precipitate was observed. The mixture was set aside at room temperature for 3 h. The solid was separated, dried, and recrystallized from toluene.

Reduction of 2-[1,3-*Di*(*benzotriazol*-1-*yl*)*butylamino*]*pyridine* (**20**) *with Sodium Borohydride.*—The reduction was carried out applying procedure A but double the amount of sodium borohydride was used. Crude 2-[3-(benzotriazol-1-yl)butylamino]-pyridine (**21**) (95%) was obtained as an oil; δ($CDCl_3$) 1.73 (3 H, d, *J* 6.94 Hz), 2.52 (2 H, m), 3.30 (2 H, m), 5.19 (1 H, m), 6.36 (1 H, d, *J* 9.0 Hz), 6.64 (1 H, t, *J* 6.4 Hz), 7.56 (4 H, m), and 8.19 (3 H, m). The product was further characterized as its picrate (see Table 2).

References

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