FORMATION OF (*N*-HETEROARYL)HETEROARYLMETHANAMINES FROM HETEROAROMATIC ALDEHYDES AND HETEROAROMATIC AMINES°

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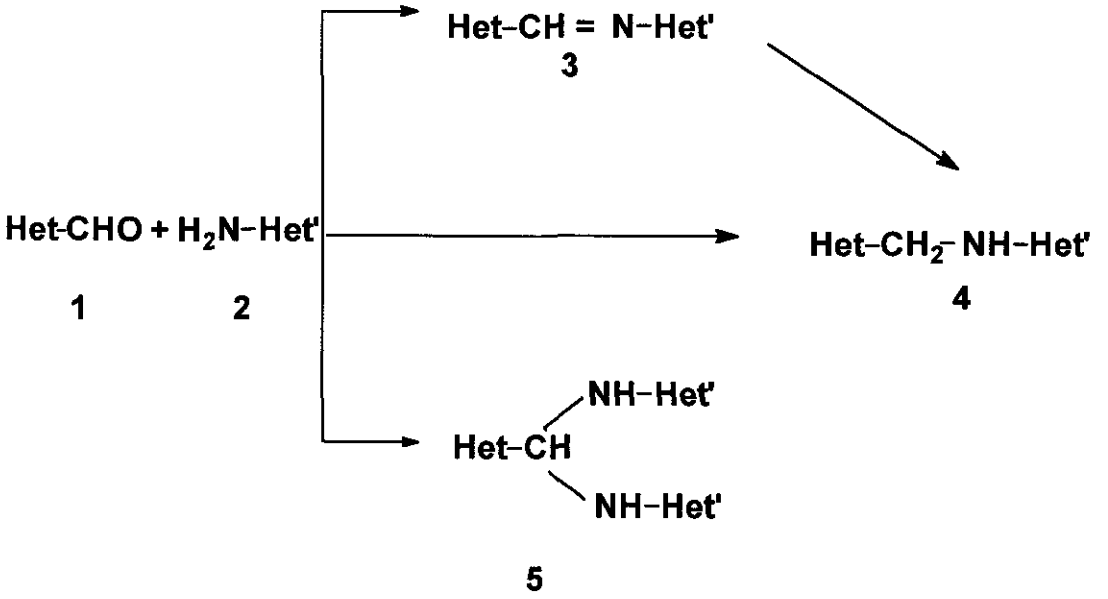
Abstract- The reactions of heteroaromatic aldehydes with heteroaromatic amines show significant differences depending on the heteroaromatic moieties present both in the aldehydes and in the amines, giving imines **(3)** or [bis-(heteroarylamino)methyl]arenes **(5)**. The direct formation of (*N*-heteroaryl)heteroarylmethanamines **(4)** is achieved by the Leuckart-Wallach reaction. Reaction conditions for the formation of amines **(4)** by $NaBH_4$ reduction of imines **(3)** are also reported.

The reaction of aromatic aldehydes with primary amines to give imines usually called Schiff bases has longly been known. [1] Recent work on the reactions of 2-aminothiazoles with aromatic aldehydes[2] pointed out that the above reactions are highly dependent on the various amine-aldehyde pairs and that formation of only [bis-(heteroarylamino)methyl]arenes can be observed.

A wider study aimed at the design of (*N*-heteroaryl)heteroaromatic methanamines in order to compare their antimycotic activity with that of analogous substituted (*N*-heteroaryl)benzylamines,[3] required the synthesis of heteroaromatic secondary amines. The planned reaction sequence, *i.e.* condensation of aromatic aldehydes with

° Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

heteroaromatic amines followed by $NaBH_4$ reduction of the Schiff bases, turned out to be not straightforward owing to wide divergencies depending on the aromatic moieties present both in the aldehydes and in the amines. In the present work we report the reactivity of heteroaromatic aldehydes **(1)** with heteroaromatic amines **(2)** with the aim to develop suitable synthetic methods for the formation of (*N*-heteroaryl)heteroarylmethanamines **(4)** and to compare them with previous work in the field.



Het	Het'
a. 2-Thienyl	f. 2-Thiazolyl
b. 3-Indolyl	g. 3-Quinolyl
c. 2-Furyl	h. 2-Pyrimidyl
d. 2-Pyridyl	i. 2-Benzothiazolyl
e. 2-Quinolyl	

RESULTS AND DISCUSSION

Comparison of Synthetic Methods

Among the methods used most frequently for the synthesis of imines, we selected heating of the reagents in ethanol[4,5] (Method A) and refluxing in acetone[2] (Method B). The azeotropic removal of water by boiling solutions with benzene[6] or toluene was not pursued due to the formation of dark mixtures and to the low product yields.[2] Heating in formic acid (Method C) was also tried in a few cases.

Table 1. Preparation of products **(3)**, **(4)** and **(5)** by Methods A-C

Reactants	Product	Het	Het'	Method	Time (h)	Yield (%)
1a + 2f	**5af**	2-Thienyl	2-Thiazolyl	A	10	6*
1a + 2f	**3af**	2-Thienyl	2-Thiazolyl	B	4	23
1a + 2h	**5ah**	2-Thienyl	2-Pyrimidyl	A	1.5	72
1a + 2h	**5ah**	2-Thienyl	2-Pyrimidyl	B	1.5	57
1a + 2h	**4ah**	2-Thienyl	2-Pyrimidyl	C	7	45
1b + 2i	**3bi**	3-Indolyl	2-Benzothiazolyl	A	9	49
1c + 2i	**3ci**	2-Furyl	2-Benzothiazolyl	A	9	60
1d + 2h	**5dh**	2-Pyridyl	2-Pyrimidyl	A	0.33	84
1d + 2h	**5dh**	2-Pyridyl	2-Pyrimidyl	B	0.33	81
1d + 2h	**---**	2-Pyridyl	2-Pyrimidyl	C	9	---
1e + 2g	**3eg**	2-Quinolyl	3-Quinolyl	A	0.33	76
1e + 2f	**polymer**	2-Quinolyl	2-Thiazolyl	A	0.5	---
1e + 2f	**polymer**	2-Quinolyl	2-Thiazolyl	B	0.5	---

* Yields established by ^{1}H-nmr; products were not isolated in this experiment.

Method A afforded imines **(3bi)**, **(3ci)** and **(3eg)** in satisfactory yields, but the reaction of 2-thiophenealdehyde **(1a)** with 2-thiazolamine **(2f)**, gave only small quantities of bisamine **(5af)** together with unreacted amine **(2f)**.

The presence of imines and/or bisamines in the reaction mixtures could easily be evidenced by the characteristic CH protons in the nmr spectra occurring at 8.8-9.2 ppm for imines **(3)** and at 6.1-6.5 ppm for bisamines **(5)**. The marked tendency of thiazolamine to form bisamines has been reported.[2] Bisamines formation is probably due to stabilization of the intermediate carbinolamine by the protic solvent, allowing nucleophilic attack by a second amine molecule **(2f)** to give **(5af)**. The use of an aprotic solvent such as acetone (Method B) favoured intramolecular dehydration of the carbinolamine with formation of imine **(3af)**.

In the reaction of **1a** with the less reactive 2-pyrimidineamine **(2h)** both Methods A and B gave bisamine **(5ah)** in 72% and 57% respective yields, consistent with the above-mentioned carbinolamine stabilization. Direct formation of the desired amine **(4ah)** was then achieved by reacting **1a** and **2h** in the presence of formic acid under Leuckart-Wallach conditions (Method C). The latter reaction has longly been known,[7] widely applied in organic synthesis and mechanistically investigated; a radical mechanism[8] and more recently rate limiting C-H bond cleavage[9] have been proposed.

In the reaction of 2-pyridinealdehyde **(1d)** with 2-pyrimidineamine **(2h)** both Methods A and B gave bisamine **(5dh)** in higher yields as compared with the thiophene analogue **(5ah)**, in agreement with the higher electrophilic character of the carbon atom attached to a pyridine ring. The Leuckart-Wallach reaction of **1d** with **2h** (Method C) afforded only polymeric products. Other reductive amination methods using borohydride[10] and cyanoborohydride[11] are under investigation.

Table 1 shows that the reaction of heteroaromatic aldehydes **(1)** with amines **(2)** are highly sensitive to the nature of heteroaromatic moieties present in the aldehydes and particulary in the amines. For the less reactive amines the use of an aprotic solvents (Method B) is advised. The Leuckart-Wallach reaction proved to be an effective alternative, but of limited application.

Although generalization of the reactivity is difficult at the present stage, the above guidelines may be adopted in the reaction of heteroaromatic aldehydes with heteroaromatic amines for the formation (*N*-heteroaryl)heteroarylmethanamines **(4)**.

The reduction of **3** to the corresponding **4** was performed by treatment with $NaBH_4$ in methanol.

The main spectroscopic features of amines **(4)**, reported in Table 2, are consistent with those of *N*-benzylaniline.[12-14]

Table 2. Characterization of **amines (4)** by ir, nmr and mass spectra.

Compound	Ir (cm^{-1})			^{1}H-Nmr (ppm)		^{13}C-Nmr (ppm)	Mass Spectra m/z (%)		
	NH	CH *sym.*	CH *as.*	$C\underline{H}_2$	N$\underline{H}$	$\underline{C}H_2$	M^+	Het-CH_2^+	Het'-NH^+
4af	3380	2950	2915	4.66(d,J=0.7 Hz)	6.07	49.51	196(37)	97 (100)	99 (5)
4ah	3440	2980	2920	4.80 (dd, J=5.9 Hz, J= 0.8 Hz)	5.70	46.32	191(100)	97 (53)	---
4bi	3420	2895	2820	4.80 (d, J=0.4 Hz)	5.62	48.26	279(25)	130(100)	149 (80)
4ci	3175	2880	2835	4.62 (s)	6.45	49.34	230(98)	81 (100)	149 (9)
4eg	3360	3055	3030	4.45 (s)	5.42	46.92	285(100)	142 (23)	143 (25)

EXPERIMENTAL

Melting points are uncorrected. Ir spectra (KBr discs) were recorded on a Perkin Elmer 684 spectrophotometer. Nmr spectra were recorded at 200 MHz on a Bruker spectrometer (TMS as internal standard) using $CDCl_3$ as solvent.

The mass spectra were recorded by direct insertion into a VG-ZAB 2SE double focusing mass spectrometer under the following conditions: ionization energy 70 eV; source temperature 200°C; trap current 100 A; acceleration voltage 8KV; sample temperature 30°C; resolution 1500.

Method A. A solution of the aldehyde **(1)** and of the amine **(2)**, (equimolar amounts, 10 mmol), was refluxed in 10 ml of dry ethanol. The time required varied from few min to 9 h (see Table 1), depending upon the basicity of the amine. The solvent was evaporated under reduced pressure and the composition of the residue was examined by t l c. The crude imines thus obtained were crystalline and in some cases, due to their low stabilities, they were not purified before reduction. Mixtures of $CHCl_3$/petroleum ether (bp 40-70°C) were used as crystallization solvent.

Method B. Acetone was used instead of dry ethanol in Method A and the mixture was refluxed for the appropriate time (see Table 1).

Method C. Equimolar amounts of the aldehyde and of the amine (10 mmol) were refluxed in 10 ml of formic acid. The solution was cooled and made alkaline to litmus with 20% KOH, the product was extracted with ether, converted to the hydrochloride and precipitated with solid Na_2CO_3..

Reduction of imines 3. A solution or suspension of the imine (10 mmol) in methanol (10 ml) was treated with sodium borohydride (20 mmol) and the mixture was heated on a steam bath for 2 h with stirring, until the reagent was consumed and most of the methanol was evaporated. The reaction mixture was then cooled and treated with water. The product was washed with water and crystallized from ethanol.

2-(2-Thienilideneamino)thiazole (3af): Yield 23%. White prisms. mp 82-83°C, lit.,[2] 79-80°C.

2-(3-Indolideneamino)benzothiazole (3bi): Yield 49%. Yellow microcrystals. mp 69-71°C. Ms *m/z* (%): 277 (M^+, 100), 144 (13), 143 (23), 134 (21).

2-(2-Furylideneamino)benzothiazole (3ci): Yield 60%. White needles. mp 102-104°C. Ms *m/z* (%): 228 (M^+, 100), 130 (22), 91 (25).

3-(2-Quinolinideneamino)quinoline (3eg): Yield 76%. Yellow prisms. mp 168-169°C. Ms *m/z* (%): 283 (M^+, 100), 155 (39), 128 (47).

2-[(Thiophen-2-ylmethyl)amino]thiazole (4af): Yield 80%. White needles. mp 110°C. Ms *m/z* (%): 196 (M^+, 37), 97 (Het-CH_2^+, 100). Ir (KBr): 3380 (NH). ^{1}H-Nmr δ: 4.66 (C$\underline{H}_2$, 2H, d, J=0.7 Hz), 6.07 (N$\underline{H}$, 1H, s), 6.51 (1H, d, J=3.7), 6.97 (1H, dd, J=4.9, J=3.6), 7.04 (1 H, ddt, J=3.6, J=1.3, J=0.7) 7.07 (1H, d, J=3.6) 7.25 (1H, dd, J=4.9, J=1.3).

2-[(Thiophen-2-ylmethyl)amino]pyrimidine (4ah): Yield 45% (Method C). White microcrystals. mp 95°C. Ms *m/z* (%): 191 (M^+, 100), 112 (20), 97 (Het-CH_2^+, 53). Ir (KBr): 3440 (NH). ^{1}H-Nmr δ: 4.80 (C$\underline{H}_2$, 2H, dd, J=5.9 Hz, J=0.8 Hz), 5.70 (N$\underline{H}$, 1H, s), 6.6 (2H, t, J=4.8), 6.95 (1H, dd, J=4.9, J=3.74), 7.02 (1H, ddt, J=3.7, J=1.5, J=0.8), 7.21 (1H, dd, J=4.9, J=1.5), 8.3 (2H, d, J=4.8).

2-[(Indol-3-ylmethyl)amino]benzothiazole (4bi): Yield 78%. White microcrystals. mp 184-185°C , lit.[15] 186°C .

2-[(Furan-2-ylmethyl)amino]benzothiazole (4ci): Yield 78%. White needles. mp 119-121°C. Ms *m/z* (%): 230 (M^+, 98), 81 (Het-CH_2^+, 100). Ir (KBr): 3175 (NH). ^{1}H-Nmr δ: 4.62 (C$\underline{H}_2$, 2H, s), 6.45 (N$\underline{H}$, 1H, s), 6.32 (2H, m), 7.08 (1H, ddd, J=6.6, J=6.7, J=1.3), 7.28 (1H, ddd, J=6.7, J=7.7, J=1.3), 7.57 (1H, ddd, J=6.6, J=1.2, J=0.6).

3-[(Quinolin-2-ylmethyl)amino]quinoline (4eg): Yield 80%. White microcrystals. mp 190-192°C. Ms *m/z* (%): 285 (M^+, 100), 284 (M^+-1, 100), 143 (25), 142 (Het-CH_2^+, 23). Ir (KBr): 3360 (NH). ^{1}H-Nmr δ: 4.45 ($C\underline{H}_2$, 2H, s), 5.42 (N$\underline{H}$, 1H, s), 8.86-9.20 (2H, m), 7.5-8.5 (10 H, m).

2-[Bis(pyrimidin-2-ylamino)methyl]thiophene (5ah): Yield 72% (Method A), 57% (Method B). White microcrystals. mp 156-157°C. Ms *m/z* (%): 284 (M^+, 100), 189 (56), 94 (15).

2-[Bis(pyrimidin-2-ylamino)methyl]pyridine (5dh): Yield 84% (Method A), 81% (Method B). White microcrystals. mp 202°C. Ms *m/z* (%): 279 (M^+, 100), 185 (79), 94 (21).

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