Reaction of Symmetric N^1,N^2-Diarylamidines with α-Bromoacetophenone and Ethyl 2-Bromoethanoate†

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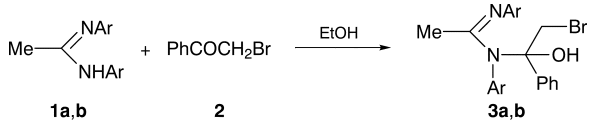
2-Bromo-1-{aryl[1-(arylimino)ethyl]amino}-1-phenylethanol derivatives **3a**, **3b** were obtained from the reaction of N^1,N^2-diarylacetamidines **1a**, **1b** with α-bromoacetophenone **2**, while **1a**, **1b** with ethyl 2-bromoethanoate **4** afforded 2-{[1-(arylimino)]ethyl}aminoethanoic acid derivatives **5a**, **5b**; N^1,N^2-diarylformamidines **6a**, **6b** reacted with **2** and **4** to give the arylaminoacetophenones **8a**, **8b** and *N*-arylglycine ethyl esters **11a**, **11b** respectively together with the corresponding formanilides **9a**, **9b**.

N^1,N^2-Disubstituted formamidines condensed with active methylene compounds leading to enamines and the corresponding free amines.[1] This condensation was utilized to synthesize quinoline derivatives by treating N^1,N^2-diarylformamidines with ethyl malonate.[2] On the other hand β-cyanoesters condensed with free acetamidines to give 2-amino-4-hydroxypyridine.[3] Previously it was reported that *N*,*N*,*N*′-triarylamidines when treated with tetrahalogenobenzoquinones underwent cleavage into 2-(arylamino)-3,5,6-trihalogeno-1,4-benzoquinones and their 2,5-bis(arylamino) analogues together with the corresponding formanilides.[4] N^1,N^2-Diarylformamidines reacted with dichloro-1,4-naphthoquinone (DC1NQ) and tetrachlorobenzoquinone (CHL) to give 2-(arylamino)-3-(formylarylamino)-1,4-naphthoquinones and benzimidazolinones respectively as substitution products.[5] On the other hand N^1,N^2-diarylacetamidines reacted with DC1NQ and CHL to afford the new chiral compounds 3-aryl-2-(arylimino)-9b-hydroxy-1*H*-benz[*e*]indol-5-ones and 1-aryl-2-(arylimino)-3a-hydroxy-1*H*-indol-6-ones respectively as substitution–addition products.[5] In this paper the results of the interaction of the N^1,N^2-diaryl-formamidines and -acetamidines with α-bromoacetophenone and ethyl 2-bromoethanoate are presented.

N^1,N^2-Diarylacetamidines have two reactive sites for nucleophilic addition. When a solution of N^1,N^2-diarylacetamidines **1a, 1b** and α-bromoacetophenone **2** in ethanol was heated for 2 h, 2-bromo-1-{aryl[1-(arylimino)ethyl]amino}-1-phenylethanol derivatives **3a**, **3b** were isolated in 47–50% yield.

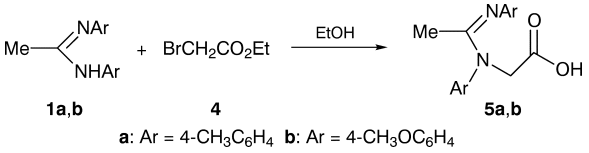


Scheme 1

The structures of the products **3a**, **3b** were assigned on the basis of their elemental analysis and spectral data. In their IR spectrum the carbonyl absorption bands were not observed but the hydroxyl absorption bands were.

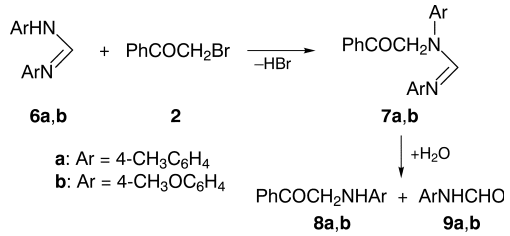
The ^{1}H decoupled ^{13}C NMR spectra revealed signals between δ 93.52 and 94.10 for an aliphatic quaternary carbon atom bearing a hydroxyl group.[6] ^{13}C DEPT spectra exhibited negative signals between δ 66.51 and 67.34 at lower field for the methylene group attached to the bromine atom. The ^{1}H NMR spectra showed AB patterns with δ_A 4.51–4.61 and δ_B 4.71–4.98 with coupling constants between 12.80 and 12.90 Hz, which indicates that a methylene group is present adjacent to a chiral carbon atom. These unexpected results indicate that the addition of the imino nitrogen atom to the carbonyl group is preferred rather than substitution on the methylene carbon atom of **2**.

On the other hand when the solutions of acetamidines **1a**, **1b** and ethyl 2-bromoethanoate **4** were heated in ethanol for 1 h, 2-{aryl[1-(arylimino)]ethyl}aminoethanoic acid derivatives **5a**, **5b** were obtained in 61–64% yield. Acids **5a**, **5b** are formed *via* a replacement of the bromine atom by the amidine molecule, followed by hydrolysis by taking up a molecule of water from the ethanol used, with liberation of an ethanol molecule. This is probably due to the presence of the liberated HBr which catalyses this hydrolysis.



Scheme 2

The structures of compounds **5a**, **5b** were assigned on the basis of the following data. Their IR spectra showed sharp bands at 3297–3295 and 1662–1660 cm^{-1} for the OH and C=O of the carboxylic group respectively. In their ^{13}C NMR spectra the characteristic signal of the carboxylic ester group at δ 166.60 was replaced by signals at δ 172.5 which are characteristic for the carboxylic acid carbon atom.[6] The replacement of the bromine atom was also confirmed from the mass spectra (m/z = 296 and 328 for **5a** and **5b** respectively) and the correct elemental analysis.

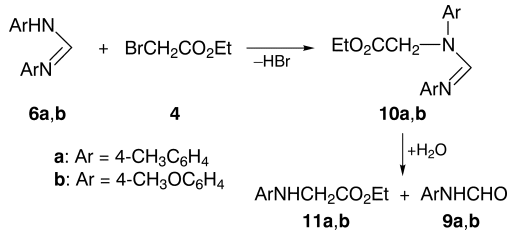


Scheme 3

N^1,N^2-Diarylformamidines **6a**, **6b** were investigated with both α-bromoacetophenone **2** and ethyl 2-bromoethanoate **4**. Heating solutions of **6a**, **6b** and **2** in ethanol for 1 h gave the arylaminoacetophenones **8a**, **8b** together with the corresponding formanilides **9a**, **9b**. The structures of **8a**, **8b**[7,8] and **9a**, **9b**[9,10] were identified by comparison of their melting points with those previously reported.

Also compound, **6a**, **6b** reacted with the ethyl 2-bromoethanoate in ethanol to afford *N*-arylglycine ethyl esters **11a**, **11b** together with the corresponding formanilides **9a**, **9b**.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 4

The structures of compounds **11a**, **11b** were identified by comparison of their melting points with those previously reported.[11] Thus it is obvious that the reaction of the formamidines with **2** and **4** replaces the bromine atom to give the intermediates **7a**, **7b** and **10a**, **10b** followed by spontaneous hydrolysis (by absorption of water from the ethanol used), probably due to the presence of the liberated HBr to **8a**, **8b**, **11a**, **11b** and **9a**, **9b** respectively.

Conclusion

N^1,N^2-Diaryl-formamidines and -acetamidines react with the bromo-active methylene derivatives by nucleophilic substitution rather than by condensation,[1–3] while acetamidines **1a, 1b** with bromoacetophenone **2** they undergo nucleophilic addition. This is probably due to electronic effects, where in the case of **2** the carbonyl group is attached to a benzene ring, which leads to faster addition than in the saturated analogues.

Experimental

General experimental details have been described previously.[12]

Reaction of N^1,N^2-Diarylacetamidines **1a**, **1b** *with α-Bromoacetophenone* **2** *and Ethyl 2-bromoethanoate* **4**.—Solutions of compounds **1a, 1b** (1.0 mmol) in ethanol (10 cm^3) were added to a solution of **2** or **4** (1.0 mmol) in ethanol (5 cm^3) and heated to reflux temperature for 1 h. The reaction mixtures were then concentrated and the residues subjected to PLC using toluene–ethyl acetate (1:2) as the developing solvent to give one main zone which contained **3a, 3b** or **5a, 5b**. The zones were extracted, crystallized and identified as follows:

2-*Bromo*-1-{(4-*methylphenyl*)[1-(4-*methylphenylimino*)*ethyl*]*amino*}-1-*phenylethanol* **3a**.—Colourless crystals (204 mg, 47%), MP 218 °C (from ethyl acetate–cyclohexane); IR (KBr) 3413 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ 2.15 (3 H, s, CH_3), 2.27 (3 H, s, CH_3 aryl), 2.41 (3 H, s, CH_3 aryl), 4.61 (1 H, d, 1a′-H), 4.98 (1 H, d, 1b′-H, $|^2J|$ 12.90 Hz, CH_2Br), 7.06, 7.32, 7.38, 7.57, 7.58 and 7.82 (13 H, all m, aryl H), 8.48 (1 H, br, OH); ^{13}C NMR ($CDCl_3$) δ 13.72 (CH_3), 21.19 (CH_3 aryl), 21.29 (CH_3 aryl), 67.34 (CH_2Br), 94.10 (COH), 126.09, 126.86, 128.57, 129.39, 129.92 and 132.85 (all aryl CH), 129.38 and 132.0 (aryl *C*CH_3), 138.98 (aryl *C*COH), 140.16 and 140.47 (aryl NC), 164.62 (C=N); MS *m*/*z* (%) 438 (M^++2, 1), 436 (M^+, 1), 393 (3), 356 (M^+-HBr, 4), 250 (25), 132 (83), 106 (100), 81 (14), 79 (10) (Found: C, 65.81; H, 5.70; N, 6.30. Calc. for $C_{24}H_{25}BrN_2O$: C, 65.91; H, 5.76; N, 6.41%).

2-*Bromo*-1-{(4-*methoxyphenyl*)[1-(4-*methoxyphenylimino*)*ethyl*]-*amino*}-1-*phenylethanol* **3b**.—Colourless crystals (234 mg, 50%), mp 205–207 °C (from ethyl acetate–cyclohexane); IR (KBr) 3414 cm^{-1} (OH); ^{1}H NMR [$(CD_3)_2SO$] δ 2.07 (3 H, s, CH_3), 3.71 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.51 (1 H, d, 1a′-H), 4.71 (1 H, d, 1b′-H, $|^2J|$ 12.80 Hz, CH_2), 6.93, 7.16, 7.27, 7.35, 7.40, 7.40, 7.73 and 7.75 (13 H, all m, aryl H), 8.48 (1 H, s, OH); ^{13}C NMR [$(CD_3)_2SO$] δ 13.61 (CH_3), 55.27 and 55.55 (OCH_3), 66.51 (CH_2Br), 93.52 (COH), 114.25, 114.88, 126.8, 127.64, 128.0, 128.92 and 129.87 (all aryl CH), 128.26 (aryl CCOH), 138.0 (aryl NC), 159.57 and 159.65 (aryl $COCH_3$), 164.63 (C=N); MS *m*/*z* (%) 471 (M^++2, 1), 469 (M^+, 1), 425 (8), 407 (34), 389 (M^+-HBr, 9), 370 (19), 283 (8), 148 (6), 136 (29), 108 (100), 81 (15), 80 (24), 79 (15) (Found: C, 61.50; H, 5.37; N, 6.35. Calc. for $C_{24}H_{25}BrN_2O_3$: C, 61.41, H, 5.37; N, 5.97%).

N-(4-*Methylphenyl*)-*N*-[1-(4-*methylphenylimino*)*ethyl*]*glycine* **5a**.—Colourless crystals (190 mg, 64%), mp 154 °C (from ethyl acetate–cyclohexane); IR 3295 (OH), 1662 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 2.12 (3 H, s, CH_3), 2.30 (3 H, s, aryl CH_3), 2.33 (3 H, s, aryl CH_3), 4.40 (2 H, s, CH_2), 7.01–7.40 (8 H, all m, aryl H), 8.70 (1 H, s, CO_2H); MS *m*/*z* (%) 296 (M^+, 70), 189 (60), 136 (20), 107 (49) (Found: C, 72.59; H, 7.24; N, 9.35. Calc. for $C_{18}H_{20}N_2O_2$: C, 72.96; H, 7.04; N, 9.45%).

N-(4-*Methoxyphenyl*)-*N*-[1-(4-*methoxyphenylimino*)*ethyl*]*glycine* **5b**.—Colourless crystals (200 mg, 61%), mp 144–145 °C (from ethyl acetate–cyclohexane); IR (KBr) 3297 (OH), 1660 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.94 (3 H, s, CH_3), 3.77 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 4.86 (2 H, s, CH_2), 6.80–4.73 (8 H, all m, aryl H), 8.62 (1 H, s, CO_2H); ^{13}C NMR ($CDCl_3$) δ 22.32 (CH_3), 55.34 (CH_2), 55.50 (OCH_3), 55.53 (OCH_3), 114.13, 115.06, 121.64 and 128.68 (all aryl H), 131.11 and 136.06 (aryl CN), 156.39 and 159.41 (aryl $COCH_3$), 172.50 (CO_2H); MS *m*/*z* (%) 328 (M^+, 28), 206 (55), 178 (21), 136 (100), 123 (50), 108 (13) (Found: C, 65.65; H, 6.10; N, 8.58. Calc. for $C_{18}H_{20}N_2O_4$; C, 65.84; H, 6.14; N, 8.53%).

Reaction of N^1,N^2-Diarylformamidines **6a**, **6b** *with α-Bromoacetophenone* **2**.—Solutions of compounds **6a, 6b** (1.0 mmol) in ethanol (10 cm^3) were added to a solution of **2** (199 mg, 1.0 mmol) in ethanol (5 cm^3) and heated to reflux temperature for 1 h. After this period yellow crystals of **8a, 8b** were precipitated which were filtered off and recrystallized from ethanol. The filtrates were concentrated and the residues subjected to PLC using toluene–ethyl acetate (10:1) as the developing solvent to give two zones. The faster moving one contained **8a, 8b** while the more slowly moving one contained **9a, 9b**. The zones were extracted, crystallized and identified as follows: α-(4-methylphenylamino)acetophenone **8a**, 90 mg (40%), yellow crystals (from ethanol), mp 126–127 °C (lit.,[7] 128–129 °C); α-(4-methoxyphenylamino)acetophenone **8b**, 88 mg (37%), yellow crystals (from ethanol), mp 90–92 °C (lit.,[8] 93 °C); 4′-methylformanilide **9a**, 61 mg (45%), colourless crystals (from light petroleum, bp 40–60 °C), mp 53 °C (lit.,[9] 52 °C); 4′-methoxyformanilide **9b**, 70 mg (46%), colourless crystals (from light petroleum), mp 83 °C (lit.,[10] 84–85 °C).

Reaction of N^1,N^2-Diarylformamidines **6a**, **6b** *with Ethyl 2-Bromoethanoate* **4**.—A solution of compound **4** (167 mg, 1.0 mmol) in ethanol (5 cm^3) was added dropwise to a solution of formamidines **6a, 6b** (1.0 mmol) in ethanol (10 cm^3) at room temperature, giving a yellow colour. The reaction mixture was left standing for 1 h, concentrated and subjected to PLC using toluene–ethyl acetate (10:1) as developing solvent to give two zones. The faster moving one contained **11a, 11b** while the second zone contained the corresponding formanilides **9a, 9b**. The zones were extracted, crystallized and identified as follows: *N*-(4-methylphenyl)glycine ethyl ester **11a**, 100 mg (52%), colourless crystals (from cyclohexane), mp 50 °C (lit.,[11] 51 °C); *N*-(4-methoxyphenyl)glycine ethyl ester **11b**, 120 mg (57%), colourless crystals (from cyclohexane), mp 58–59 °C (lit.,[11] 59 °C).

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