Syntheses of *o*-Aminohetarenecarbaldehydes via Azides

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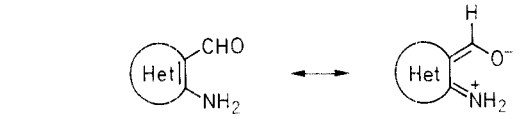
o-Chlorohetarenecarbaldehydes react with sodium azide at low temperature yielding moderately stable *o*-azidohetarenecarbaldehydes. With hydrogen sulfide these compounds are reduced to the corresponding stable *o*-amino aldehydes. Both reaction steps give high yields.

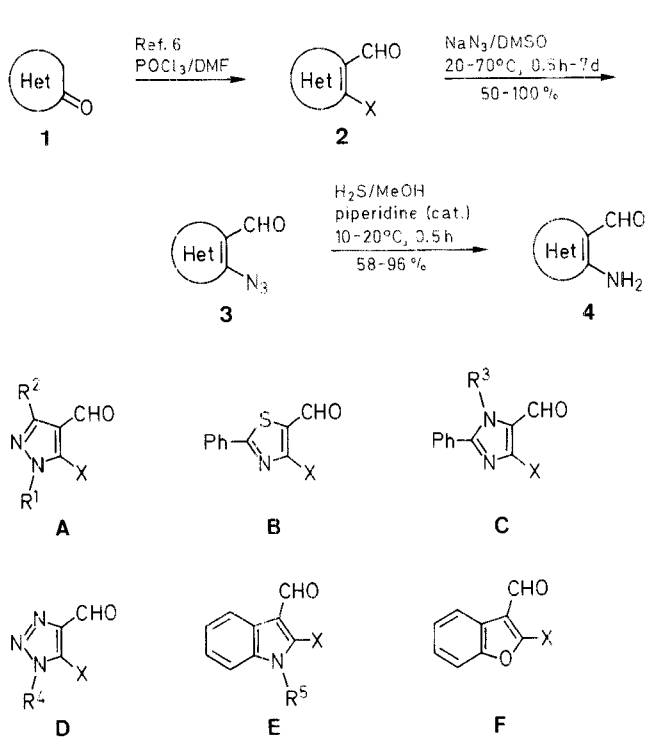
o-Aminohetarenecarbaldehydes are very useful[2] starting materials for the preparation of anulated heterocyclic systems. However, in spite of this fact, relatively few types of *o*-aminohetarenecarbaldehydes are known, and we were surprised to find only few references in the literature, specially for the parent 2-amino-3-formylindole which has only been reported[3] once as the hydrochloride which was obtained in a multistep synthesis. In some cases *o*-amino aldehydes are relative unstable compounds, e.g., *o*-aminobenzaldehyde[2] while 2-amino-3-formylquinoxaline[4] and 2-amino-3-formylpyridine[2] are heterocyclic examples, the latter being perfectly stable. However, we found that in the azole series delocalization permits an electron distribution as shown in Scheme **A** the *o*-aminohetarenecarbaldehydes show no tendency to self condensation and they may be regarded as vinylogous amides.



Scheme **A**

In the azole series the *o*-chloro aldehydes **2** can usually be prepared in high yields from the oxo compound **1** (Scheme **B**).

The starting *o*-chloro aldehydes were prepared via the Vilsmeier chloroformylation reaction as previously described,[6] however, the imidazole example **C** was prepared by another route using halogen exchange and formylation by dimethylformamide. This route has been described by Iddon and Khan[19] for the preparation of 1-benzyl-4-bromo-5-formylimidazole (**2c**), Scheme **C**. We found that the 4-bromo moiety in this 2-unsubstituted imidazole did not react with the azide anion in either dimethylformamide or dimethyl sulfoxide as the azide anion is a poor nucleophile. Therefore we introduced the 2-phenyl substituent which in fact did activate the 4-bromo moiety enough in compound **2C** to make this nucleophilic reaction possible (7 days at 60°C).



2Aa: X = Cl; **3Aa:** X = N_3; **4Aa:** X = NH_2; R^1 = CH_3; R^2 = H

2Ab: X = Cl; **3Ab:** X = N_3; **4Ab:** X = NH_2; R^1 = CH_3; R^2 = Ph

2Ac: X = Cl; **3Ac:** X = N_3; **4Ac:** X = NH_2; R^1 = Ph; R^2 = CH_3

2B: X = Cl; **3B:** X = N_3; **4B:** X = NH_2

2C: X = Br; **3C:** X = N_3; **4C:** X = NH_2; R^3 = CH_2Ph

2D: X = Cl; **3D:** X = N_3; **4D:** X = NH_2; R^4 = 4-$MeOC_6H_4$

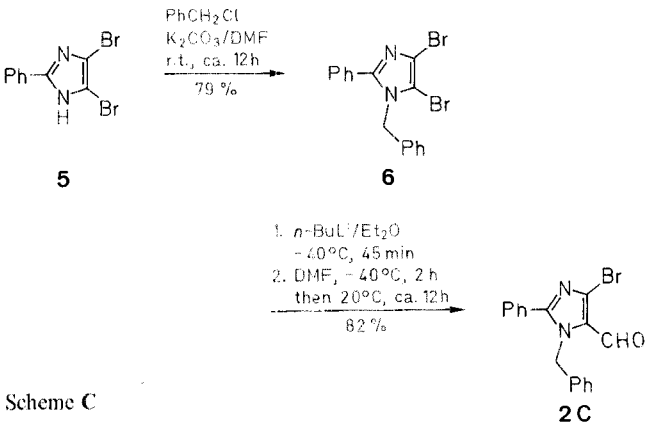
2Ea: X = Cl; **3Ea:** X = N_3; **4Ea:** X = NH_2; R^5 = CH_3

2Eb: X = Cl; **3Eb:** X = N_3; **4Eb:** X = NH_2; R^5 = CH_2Ph

2Ec: X = Cl; **3Ec:** X = N_3; **4Ec:** X = NH_2; R^5 = Ph

2F: X = Cl; **3F:** X = N_3; **4F:** X = NH_2

Scheme **B**



Scheme **C**

Under mild reaction conditions the chloro aldehydes **2** react with sodium azide in dimethyl sulfoxide to give high yields of the *o*-aldehydes **3** as the chloro atom in compound **2** is a good nucleofuge due to the activation by the formyl group.

Aubert et al.[5] have recently demonstrated the utility of this reaction in the cyclopentene series. As we had access[6] to a series of *o*-chloroformylazoles **2** it was of interest to investigate the synthesis of the corresponding azides **3** and hence the *o*-aminohetarenecarbaldehyde **4**. The *o*-azidoheterenecarbaldehydes **3**(**3Ac, 3B**, and **3D**) have recently been demonstrated[7] to be useful starting materials for the preparation of fused pyrimidines via the iminophosphoranes.

Five-membered *o*-aminohetarenecarbaldehydes have previously mainly been prepared[2] via three methods, (1) reduction of carboxylic acid derivatives such as nitriles, a method which often requires drastic reaction conditions,[8] (2) formylation of *o*-azido aldehydes. Examples of the use of method 1 can be found in the

triazole series,[9] while both method 1 and 2 have been used in the pyrazole series.[9,21] Method 3, which has found some use for the reduction of azides,[10] have been used by Gronowitz et al.[11] for the reduction of azides in the furan, thiophene, and selenophene series to the corresponding *o*-aminohetarenecarbaldehydes. In spite of the apparent versatility of this elegant method, to our knowledge it has not been used for similar reductions in other heterocyclic systems. In this paper we now report that this reduction method indeed is general and can be used for the preparation of the following potentially useful *o*-aminohetarenecarbaldehydes.

Preparation of the *o*-azido aldehydes **3** was carried out in dimethyl sulfoxide by reaction of *o*-chloro aldehydes **2** using an excess of sodium azide at a temperature < ca. 70 °C. The reaction must be monitored carefully by TLC as the use of slightly higher temperature (80–90 °C) will result in ring opening reactions.[12] The parent 2-azido-3-formylindole was not obtained as 2-chloro-3-formylindole (**2Ea**, R^5 = H) already decomposed at 0 °C under these reaction conditions. The yields of *o*-azido aldehydes are in the range 50–100% (Table 1) usually the *o*-azido aldehydes must be used immediately due to their relative thermal and photochemical instability.

Reduction of the *o*-azido aldehydes **3** was carried out by passing hydrogen sulfide into a methanol or methanol/chloroform solution containing traces of piperidine at 5–20 °C. The yields were in the range 58–96%. All the *o*-aminoaldehydes prepared are crystalline polar compounds and in the ^{13}C-NMR spectra of the 2-amino-3-formylindoles **4Ea** and **4Ec** the CHO carbons were seen as doublets at δ = 179.5; 178.8 and 179.2, 179.9, respectively. At a higher temperature (40 °C) these doublets coalesced to singlets, and this observation therefore is evidence for the presence of two forms because of hindered rotation around the C–CHO bond as this bond has double bond character. As suggested in Scheme **A** this mesomerism may well explain the stability and properties of the 2-amino-3-formylindoles. We found for example that acylation of 5-amino-4-formyl-3-methyl-1-phenylpyrazole was difficult, again an indication of a relatively low electron density, at the amino nitrogen. The ^{13}C-NMR spectrum of the 2-amino-3-formyl-1-methylindole hydrochloride showed the CHO carbon as a singlet at δ = 163.9, a chemical shift value which is found at δ = 184.8 in the parent 3-formylindole.[13]

We also tried an alternative method for the reduction of the azide function in the pyrazole series, however, without much success. In this case the triphenylphosphazene[7] obtained via the Staudinger reaction[14] only gave a dimeric product probably due to the acidic reaction conditions used.

From the results described here we conclude that the hydrogen sulfide reduction of *o*-azidohetarenecarbaldehydes is an excellent method for the synthesis of *o*-aminohetarenecarbaldehydes.

The *o*-chloroformylpyrazoles **2Aa**, **2Ab**,[6] thiazole **2B**,[6] triazole **2D**,[6] 2-chloro-3-formyl-1-benzofuran (**2F**),[15] 2-chloro-3-formyl-1-methylindole, (**2Ea**),[16] 2-chloro-3-formyl-1-phenylindole (**2Ec**),[17] 1-benzyl-2-chloro-3-formylindole (**2Eb**)[18] were prepared by reported procedures. 1-Benzyl-4-bromo-5-formyl-2-phenylimidazole (**2C**) was prepared by the general method reported by Iddon and Khan.[19] however, the reaction conditions are critical and must be controlled carefully, full experimental details are therefore included for this starting material. Preparation of *o*-azidoaldehydes **3Ac**, **3B**, and **3D** have been described in Ref. 7a.

Table 1. *o*-Azido Aldehydes **3** Prepared

Product	Yield (%) [React. Temp./ Time]	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[d] δ, J(Hz)	MS (70 eV) m/z (%)[e]
3Aa	85 [60 °C/30 h]	68–69 dec ($EtOH/H_2O$)	$C_5H_5N_5O$ (151.1)	1660 (CHO); 2150 (N_3)	3.66 (s, 3H, CH_3); 7.78 (s, 1H, H-3); 9.66 (s, 1H, CHO)	151 (M^+, 50); 123 (23); 108 (17); 43 (100)
3Ab	75 [70 °C/2.1 h]	92–94 dec ($EtOH/H_2O$)	$C_{11}H_9N_5O$ (227.2)	1669 (CHO); 2154 (N_3)	3.76 (s, 3H, CH_3); 7.30–7.75 (m, 5H$_{arom}$); 9.83 (s, 1H, CHO)	227 (M^+, 29); 199 (9); 142 (63); 43 (100)
3C	52 [60 °C/7 d]	103–105 dec[f]	$C_{17}H_{13}N_5O$ (303.3)	1657 (CHO); 2131 (N_3)	5.60 (s, 2H, CH_2); 6.90–7.70 (m, 10H$_{arom}$); 9.66 (s, 1H, CHO)	303 (M^+, 5); 275 (8); 91 (100)
3Ea	100 [20 °C/12 h]	122–123 dec (CH_2Cl_2)	$C_{10}H_8N_4O$ (200.2)	1636 (CHO); 2137 (N_3)	3.60 (s, 3H, CH_3); 7.15–7.37 (m, 3H$_{arom}$); 7.87–8.07 (m, 1H, H-4); 10.17 (s, 1H, CHO)	200 (M^+, 90); 172 (45); 143 (100)
3Eb	81 [20 °C/4 h]	96–97 dec (CH_2Cl_2)	$C_{15}H_{12}N_4O$ (276.3)	1647 (CHO); 2151 (N_3)	5.30 (s, 2H, CH_2); 7.00–7.42 (m, 8H$_{arom}$); 7.96–8.2 (m, 1H, H-4); 10.38 (s, 1H, CHO)	276 (M^+, 32); 247 (60); 219 (32); 91 (100)
3Ec	95 [20 °C/24 h]	121–122 dec (CH_2Cl_2)	$C_{14}H_{10}N_4O$ (262.3)	1641 (CHO); 2134 (N_3)	7.00–7.83 (m, 8H$_{arom}$); 8.07–8.29 (m, 1H, H-4); 10.38 (s, 1H, CHO)	262 (M^+, 12); 234 (20); 205 (100)
3F	50 [50 °C/30 min]	96–97 dec[g]	$C_9H_5N_3O_2$ (187.0)	1677 (CHO); 2142 (N_3)	7.25–7.6 (m, 3H$_{arom}$); 7.95–8.25 (m, 1H, H-4); 9.97 (s, 1H, CHO)	187 (M^+, 65); 159 (75); 131 (30); 103 (100)

[a] Uncorrected, measured on a Büchi melting point apparatus.
[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.06, N ±0.36, except for compounds **3C**, **3Ea**, **3Eb**, **3Ec**, and **3F** for which satisfactory MS peak matching were obtained.
[c] Recorded on a Perkin-Elmer 580.
[d] Obtained on a Jeol FX-60Q.
[e] Obtained on a Varian MAT 311A.
[f] Purified by preparative layer chromatography (SiO_2; petroleum ether (60–80 °C)/Et_2O; 1:2).
[g] Purified by preparative layer chromatography (SiO_2; CH_2Cl_2).

o-Azidohetarenecarbaldehydes 3; General Procedure:
A mixture of the required heterocyclic *o*-chlorocarbaldehyde **2** (5 mmol) and NaN_3 (6.5 mmol) in DMSO (15 mL) is stirred at the specified temperature (Table 1) until the disappearance of the substrate (TLC, solvent CH_2Cl_2/MeOH, 10:1). The reaction mixture is then added to water (50 mL), and the precipitated product is filtered, dried ($NaSO_4$), and recrystallized or chromatographed (Table 1).

o-Aminohetarenecarbaldehydes 4; General Procedure:
Hydrogen sulfide is introduced to a stirred suspension of the required heterocyclic *o*-azidoaldehyde **3** (2.2 mmol) in MeOH (30–70 mL) containing a few drops of piperidine during 30 min, while the temperature is maintained at 10–20 °C. The elementary sulfur which is precipitated, is filtered off and the solution is added to water (80–180 mL), whereupon cooling the *o*-aminoaldehyde **4** precipitates is filtered. An additional amount of product is obtained by extraction of the filtrate with $CHCl_3$ (3 × 25 mL). The crude *o*-aminoaldehydes **4** recrystallized or chromatographed (Table 2).

4,5-Dibromo-2-phenylimidazole (5):
This starting material is prepared according to Forsyth et al.,[20] yield: 22%; mp 156–157 °C (acetone), Lit.[20] mp 137–138 °C; total yield 46%).

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.25–7.70 (m, 3H, Ph); 7.80–8.15 (m, 2H, Ph).

MS: *m/z* (%) = 302 (M^+, 100); 221 (28); 194 (32); 104 (23).

1-Benzyl-4,5-dibromo-2-phenylimidazole (6):
A mixture of 4,5-dibromo-2-phenylimidazole **(5)** (18.1 g, 59.4 mmol) $PhCH_2Cl$ (10.72 g, 59.4 mmol), and K_2CO_3 (9.2 g, 0.066 mol) in DMF (130 mL) is stirred at r.t. overnight whereupon the reaction mixture is filtered and concentrated *in vacuo*. The resulting oil is triturated with EtOH (30 mL), and the crude crystalline product is recrystallized; yield: 18.4 g (79%); mp 91–93 °C (H_2O/MeOH, 3:7).

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.35 (2, 2H, CH_2); 7.00–7.60 (m, 10H, H_{arom}).

MS: *m/z* (%) = 392 (M^+, 68); 91 (100).

$C_{16}H_{12}Br_2N_2$	calc.	C 59.84	H 3.84	N 8.21
(392.1)	found	60.09	3.90	8.17

1-Benzyl-4-bromo-5-formyl-2-phenylimidazole (2C):
A modification of the method described by Iddon and Khan[19] is used. All equipment, solvents, etc. must be absolutely dry. Under dry nitrogen 1-benzyl-4,5-dibromo-2-phenylimidazole **(6)** (15.68 g, 0.04 mol) is dissolved in dry Et_2O (260 mL), and the mixture is cooled to −40 °C. A solution of *n*-BuLi (1.6 M in hexane, Aldrich; 30.8 mL, 0.049 mol) is added with a syringe to the stirred mixture at −40 °C over 15 min. The

Table 2. *o*-Amino Aldehydes **4** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR[c] ν(cm^{-1}) δ, *J*(Hz)	MS (70 eV) *m/z* (%)[f]
4Aa	58	156–158 (toluene/PE)	148–149[21]	1646 (CHO); 3391 (NH_2); 3314 (NH_2); 3219 (NH_2)	3.58 (s, 3H, CH_3); 6.72 (s, 2H, NH_2); 7.60 (s, 1H, H-3); 9.50 (s, 1H, CHO)	125 (M^+, 100); 124 (84); 108 (8); 81 (17); 52 (21)
4Ab	64	124–126 (toluene/PE)	$C_{11}H_{11}N_3O$ (201.2)	1631 (CHO); 3215 (NH_2); 3312 (NH_2); 3401 (NH_2)	3.69 (s, 3H, CH_3); 5.85 (s, 2H, NH_2); 7.40–7.80 (m, 5H_{arom}); 9.79 (s, 1H, CHO)	201 (M^+, 100); 200 (80); 128 (11); 81 (10)
4Ac	96	92–93 (EtOH)	97.5[8]	1650 (CHO); 3200 (NH_2); 3300 (NH_2); 3410 (NH_2)	2.40 (s, 3H, CH_3); 7.03 (s, 2H, NH_2); 7.49–7.63 (s, 5H_{arom}); 9.78 (s, 1H, CHO)	201 (M^+, 100); 200 (45); 184 (14); 174 (10)
4B	68	138–139[g]	$C_{10}H_8N_2OS$ (204.5)	1635 (CHO); 3290 (NH_2); 3400 (NH_2)	7.30–7.69 (m, 5H_{arom}); 6.00 (s, 2H, NH_2); 9.64 (s, 1H, CHO)	204 (M^+, 100); 159 (10); 104 (99); 77 (12)
4C	78	174–175[h]	$C_{17}H_{15}N_3O$ (277.3)	1641 (CHO); 3177 (NH_2); 3421 (NH_2)	5.37 (s, 2H, CH_2); 5.83 (s, 2H, NH_2); 6.96–7.60 (m, 10H_{arom}); 9.34 (s, 1H, CHO)	277 (M^+, 80); 186 (55); 91 (100)
4D	72	184–185 (EtOH/H_2O)	$C_{11}H_{12}N_4O_2$ (232.2)	1660 (CHO); 3360 (NH_2); 3480 (NH_2)	3.75 (s, 3H, CH_3); 5.42 (s, 2H, CH_2); 6.95 (d, 2H_{arom}, *J* = 8); 7.25 (d, 2H_{arom}, *J* = 8); 7.15 (s, 2H, NH_2); 9.85 (s, 1H, CHO)	232 (M^+, 12); 203 (12); 121 (100)
4Ea	94	197–198 (EtOH)	$C_{10}H_{10}N_2O$ (174.2)	1641 (CHO); 3357 (NH_2); 3181 (NH_2)	3.57 (s, 3H, CH_3); 6.86–7.33 (m, 4H_{arom}); 7.66 (s, 2H, NH_2); 9.86 (s, 1H, CHO)	174 (M^+, 100); 157 (10); 129 (6)
4Eb	77	205–207 (PE)	$C_{16}H_{14}N_2O$ (250.3)	1626 (CHO); 3370 (NH_2); 3180 (NH_2)	5.37 (s, 2H, CH_2); 6.95–7.47 (m, 9H_{arom}); 7.75 (s, 2H, NH_2); 9.93 (s, 1H, CHO)	250 (M^+, 75); 221 (4); 91 (100)
4Ec	82	162–164 (EtOH)	$C_{15}H_{12}N_2O$ (236.3)	1636 (CHO); 3171 (NH_2); 3372 (NH_2)	6.77–8.00 (m, 11H_{arom} and NH_2); 10.0 (s, 1H, CHO)	236 (100); 206 (10)
4F	81	193–194 (EtOH)	$C_9H_7NO_2$ (161.2)	1699 (CHO); 1656 (CHO); 3182 (NH_2)	6.9–7.47 (m, 3H_{arom}); 7.63–7.88 (m, 1H, H-4); 9.94 (s, 1H, CHO)	161 (M^+, 100); 132 (20)

[a] Uncorrected, measured on a Büchi melting point apparatus; PE = petroleum ether, 60–80 °C.

[b] Satisfactory microanalyses obtained: C ± 0.05, H ± 0.05, N ± 0.34. Compound **4C** crystallized with 1/4 mol of water:
$C_{11}H_{12}N_4O_2 \cdot 1/4H_2O$ calc. C 72,45 H 5.54 N 14.91
found C 72.36 H 5.46 N 14.99.

[c] Recorded on a Perkin-Elmer 580.

[d] Solvent used: **4Ac**, **4B**, DMSO, all others $CDCl_3$.

[e] Obtained on a Jeol FX-60Q.

[f] Obtained on a Varian MAT 311A.

[g] Purified by layer chromatography (SiO_2; Et_2O/CH_2Cl_2/PE; 1:1:1).

[h] Purified by layer chromatography (SiO_2; CH_2Cl_2/MeOH; 30:1).

stirring is continued for 30 min, whereupon dry DMF (8 mL, 0.103 mol) is added at −40 °C, and the mixture is stirred at this temperature for 2 h. The cooling is discontinued, and the temperature is allowed to raise to 20 °C, and the mixture is then stirred overnight. NH_4Cl (240 mL, 10%) is added and the aqueous phase is extracted with Et_2O (600 mL) whereupon the combined ether extracts are dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product is recrystallized to give 11.24 g (82%); mp 94–95 °C ($EtOH/H_2O$, 2:1).

^{1}H-NMR ($CDCl_3$/TMS): δ = 5.6 (s, 2H, CH_2); 6.90–7.65 (m, 10H, H_{arom}); 9.81 (s, 1H, CHO).

IR (KBr): ν = 1671 cm^{-1} (CHO).

MS: *m/z* (%) = 342 (M^+, 12); 340 (12); 91 (100).

$C_{17}H_{13}BrN_2O$	calc.	C 49.01	H 3.08	N 7.14
(341.2)	found	49.25	3.09	7.23

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