Lewis Acid Catalysed Cyclisation and Halogen Exchange Reactions of 1,1′-Biphenyl-2-yl Isocyanide Dihalides

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1,1′-Biphenyl-2-yl isocyanide dichloride and dibromide undergo unprecedented intramolecular Friedel–Crafts type cyclisation reactions catalysed by various Lewis acids affording useful synthetic methods for otherwise difficult to access 6-chloro- and 6-bromo-phenanthridines; nucleophilic displacement reactions of the latter and halogen exchange reactions of 1,1′-biphenyl-2-yl isocyanide dichloride and dibromide are also described.

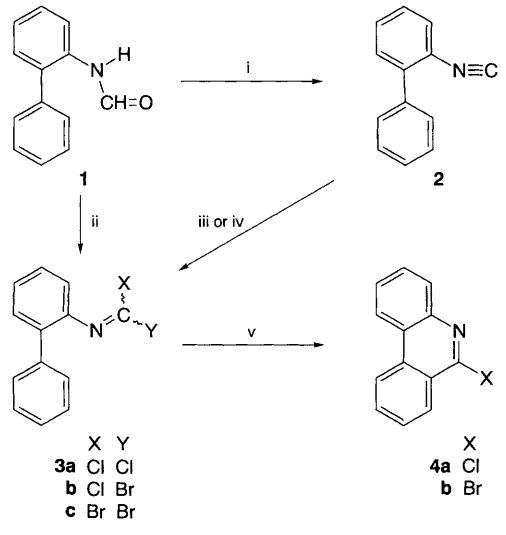
Isocyanide dihalides are readily accessible by the reaction[1,2] of isocyanides with sulphuryl chloride (isocyanide dichlorides) and bromine (isocyanide dibromides) and the chemical reactivity of these potentially useful synthetic intermediates is well documented.[2,3] However, though isocyanide dihalides are known[3] to undergo intermolecular Friedel–Crafts type reactions, analogous intramolecular processes do not appear to have been reported. Such processes would be of substantial synthetic value in affording potentially general access to cyclic imidoyl halides capable of further diverse synthetic exploitation. We now describe the efficient, Lewis acid catalysed conversion (Scheme 1) of 1,1′-biphenyl-2-yl isocyanide dichloride **3a** and dibromide **3c** into 6-chloro- and 6-bromo-phenanthridine **4a** and **4b** respectively. These heterocyclisation reactions represent the first reported examples of intramolecular Friedel–Crafts type transformations of isocyanide dihalides into cyclic imidoyl halides capable of further synthetic manipulation through nucleophilic substitution as illustrated for 6-bromophenanthridine **4b**. The previously undocumented propensity for isocyanide dihalides to undergo halogen exchange reactions is also described.

1,1′-Biphenyl-2-yl isocyanide dichloride **3a** was readily accessible[1,4] in essentially quantitative yield as a moisture sensitive oil, either directly by the low temperature (−10 °C) reaction of the known[5,6] 1,1′-biphenyl-2-yl isocyanide **2** with sulphuryl chloride in dichloromethane (Scheme 1) or by the 'one pot' sequential reaction of *N*-(1,1′-biphenyl-2-yl)formamide **1** with thionyl chloride then sulphuryl chloride. The previously undescribed† 1,1′-biphenyl-2-yl isocyanide dibromide **3c** was obtained in quantitative yield as a cream solid, mp 53–54 °C, by the low temperature (−10 °C) reaction of the isocyanide **2** with bromine in dichloromethane.

Treatment of the isocyanide dichloride **3a** with 2 equiv. of aluminium trichloride in dichloromethane at room temperature for 2 h gave the known[7] 6-chlorophenanthridine **4a** in high yield (Table 1). Titanium tetrachloride also catalysed the same transformation in comparable yield but required elevated temperature, and applied in a 'one pot' procedure with thionyl chloride and sulphuryl chloride achieved the conversion of *N*-(1,1′-biphenyl-2-yl)formamide **1** into 6-chlorophenanthridine **4a** in high overall yield (Table 1). In contrast, the more powerful Lewis acid antimony pentachloride effected the efficient cyclisation of the isocyanide dichloride **3a** to 6-chlorophenanthridine **4a** at a temperature as low as −10 °C. These unprecedented Lewis acid catalysed heterocyclisation reactions exemplify a simple and potentially general method for the synthesis of the previously difficult to access[7] 6-chlorophenanthridine **4a** and its congeners, useful synthetic intermediates in the phenanthridine series.

The isocyanide dichloride **3a** was recovered unchanged in quantitative yield after attempted cyclisation using boron trichloride in dichloromethane under conditions which succeeded with aluminium trichloride, titanium tetrachloride and antimony pentachloride indicating specific catalysis by these reagents. In addition attempted electrophilic catalysis of the cyclisation of the isocyanide dichloride **3a** using silver tetrafluoroborate was only partially successful, giving 6-chlorophenanthridine **4a** only in low yield (Table 1).

The Lewis acid catalysed cyclisation reactions of the isocyanide dibromide **3c** closely paralleled those of the isocyanide dichloride **3a**. Reaction with 2 equiv. of aluminium tribromide in dichloromethane at −10 °C afforded the known[8] 6-bromophenanthridine **4b** in high yield (Table 1). The milder conditions of this reaction presumably reflect the anticipated readier ionisation of the isocyanide dibromide **3c** compared with the isocyanide dichloride **3a** as well as the greater potency of aluminium tribromide as a Lewis acid compared with aluminium trichloride. The cyclisation of the isocyanide dibromide **3c** to 6-bromophenanthridine **4b** was also catalysed



Scheme 1 *Reagents and conditions*: i, PPh_3, CCl_4, Et_3N, $Cl(CH_2)_2Cl$, 60 °C; ii, $SOCl_2$, SO_2Cl_2, room temp. then 80 °C; iii, SO_2Cl_2, CH_2Cl_2, −10 °C; iv, Br_2, CH_2Cl_2, −10 °C; v, see Table 1

Table 1

Substrate	Catalyst/reaction conditions[a]	Product	Yield (%)[b]
3a	$AlCl_3$[c]	**4a**	84 (100)
3a	$TiCl_4$[d]	**4a**	77
1	$TiCl_4$[e]	**4a**	94
3a	$SbCl_5$[f,g]	**4a**	80
3a	$AgBF_4$[f,h]	**4a**	5
3c	$AlBr_3$	**4b**	80 (94)
3c	$TiBr_4$[i]	**4b**	17 (53)
3c	$TiBr_4$[f,j]	**4b**	93
3c	$AgBF_4$[f,h]	**4b**	60 (82)
3c	$AlCl_3$[f]	**4a** + **4b**[k]	79
3c	$TiCl_4$[l]	**4a** + **4b**[k]	100
3c	$SnCl_4$[f]	**3a**	100

[a] 2 equiv. of catalyst were used in dichloromethane at −10 °C for 2 h unless otherwise specified. [b] Yields are unoptimised; figures in parenthesis refer to yields based on unrecovered starting material. [c] Room temp. [d] Reflux. [e] **3a** Generated *in situ* from **1** and $SOCl_2/SO_2Cl_2$ then cyclised under reflux for 4 h. [f] 1 equiv. of catalyst. [g] Reaction time 0.5 h. [h] In dichloroethane. [i] Reflux 4 h. [j] Reflux 24 h. [k] Co-crystalline 2:1 mixture of **4a** and **4b** analysed by elemental combustion analysis. [l] 5 equiv. of catalyst.

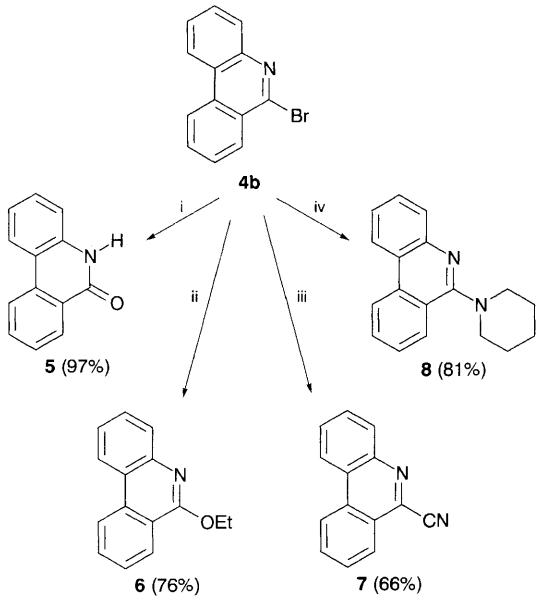
by titanium tetrabromide but under similar conditions much less efficiently (Table 1) than titanium tetrachloride in the cyclisation of the isocyanide dichloride **3a** to 6-chlorophenanthridine **4a** (see earlier). However for reasons not clearly understood at present, the reduction of the substrate to catalyst ratio and extension of the reaction time resulted in a marked improvement in the efficiency of the titanium tetrabromide catalysed process (**3c** → **4b**) (Table 1). As in the case of the failure of boron trichloride to catalyse the cyclisation of the isocyanide dichloride **3a**, boron tribromide was equally ineffective in the cyclisation of the isocyanide dibromide **3c**. On the other hand silver tetrafluoroborate effected the cyclisation (**3c** → **4b**) in good yield (Table 1). This result contrasts with the inefficiency of the silver tetrafluoroborate catalysed cyclisation of the isocyanide dichloride **3a** and again indicates the less ready ionisation of the latter compared with the isocyanide dibromide **3c**.

The Lewis acid catalysed cyclisation reactions of the isocyanide dibromide **3c** to 6-bromophenanthridine **4b** provide simple and efficient methods for the synthesis of this previously difficultly accessible[8] and hence little studied phenanthridine derivative. They also exemplify potential methods allowing general access to 6-bromophenanthridines whose importance as synthetic intermediates in the phenanthridine series is illustrated by the previously undescribed propensity for 6-bromophenanthridine **4b** to undergo nucleophilic substitution reactions exemplified in Scheme 2.

The attempted cyclisation of the isocyanide dibromide **3c** using either aluminium trichloride or titanium tetrachloride in dichloromethane at −10 °C gave high yields (Table 1) of a 2 : 1 mixture of the chloro- and bromo-phenanthridines **4a** and **4b**. The halogen exchange implicit in these transformations could occur before or after heterocyclisation. Prior halogen exchange is indicated by the finding that treatment with stannic chloride in dichloromethane at −10 °C fails to effect the cyclisation of the isocyanide dibromide **3c** but instead converts it in high yield (Table 1) into the isocyanide dichloride **3a**. The same result was achieved by treating the isocyanide dibromide **3c** with 4 equiv. of sulphuryl chloride in dichloromethane at −10 °C. However the use of 1 equiv. of sulphuryl chloride under the same conditions resulted in partial halogen exchange giving a good yield of an inseparable mixture‡ of the isocyanide dichloride **3a** and the isocyanide bromo chloride **3b**. Analogous partial halogen exchange was observed when the isocyanide dibromide **3c** was reacted with 4 equiv. of benzyltriethylammonium chloride in dichloromethane at −10 °C and interestingly, also, under similar conditions from the reaction of the isocyanide dichloride **3a** with bromine. In contrast, the isocyanide dichloride **3a** was inert to reaction with tetrabutylammonium bromide in dichloromethane at −10 °C again supporting the less ready ionisation of the isocyanide dichloride **3a** compared with the isocyanide dibromide **3c**. The halogen exchange reactions of the isocyanide dichloride **3a** and the isocyanide dibromide **3c** represent apparently previously unrecorded[3] behaviour of isocyanide dihalides, the precise mechanism(s) of which await the outcome of further investigations in this area.

We thank the SERC for a research studentship.

Received, 24th August 1995; Com. 5/05616K



Scheme 2 *Reagents and conditions*: i, 40% *w/v* $PhCH_2N^+Me_3\ OH^-$, H_2O, dioxane, reflux; ii, NaOEt, EtOH, reflux; iii, NaCN, DMF, 100 °C; iv, piperidine, MeCN, reflux

Footnotes

† Satisfactory elemental combustion analyses and mass, IR, and ^1H NMR spectral data were obtained for all new compounds.

‡ The mixture of the isocyanide dichloride **3a** and the isocyanide bromo chloride **3b** was analysed by HRMS.

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