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DOTTADs — readily made novel metal ligands with multivariant functionality and chirality

Andrea Arany, Otto Meth-Cohn * and Miklós Nyerges

Chemistry Department, University of Sunderland, Sunderland SR1 3SD, UK

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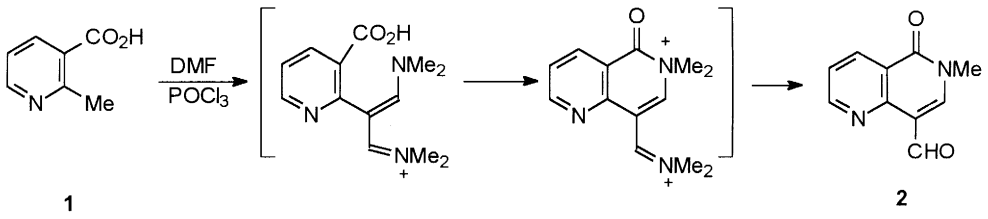
Abstract

A variety of novel ligands have been generated by Vilsmeier formylation of Hantzsch pyridines. These compounds which we call DOTTADs contain two aldehyde, imine or amine functions flanking a central pyridine nitrogen and can be homochiral or crown derivatives. The synthesis and manipulation of these systems is discussed.

Some years ago we described[1] a new cyclisation whereby *ortho*-methylarenecarboxylic acids (e.g. **1**) in which the methyl group was 'activated', underwent diformylation at the methyl group with a Vilsmeier reagent ($Me_2N{=}CHCl^+\ X^-$) followed by intramolecular acylation at the introduced nitrogen and subsequent demethylation to generate a fused pyridone-aldehyde (e.g. **2**, Scheme 1). This reaction proved quite general, the activation being effected by a conjugated nitro-group, a pyridine ring nitrogen or even an α-carboxylic acid group (e.g. homophthalic acid).



1 **2**

Scheme 1.

In this paper we show that the reaction is a highly efficient and versatile route to very useful ligands with novel potential. Thus, the compounds **2** and their congeners are themselves effective ligands for group I metals (possibly by use of the ring N and the aldehyde-hydrate). We have focused in particular on the readily available Hantzsch pyridinecarboxylic acids **6**. Formylation results in bis-cyclisation to generate a novel system **4** (Table 3) which also shows a number of interesting variants, and the products

* Corresponding author. E-mail: otto.meth-cohn@sunderland.ac.uk (O. Meth-Cohn)

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thereby derived are collected in Tables 1 and 2. We refer to these compounds as DOTTADs from the name of the parent system **8** (1,8-dioxo-1,2,7,8-tetrahydro-2,7,10-triazaanthracene-4,5-dicarbaldehydes). Several synthetic features deserve comment:

– The one-pot synthesis[2] proceeds readily and in high yield. It proceeds just as well if the Hantzsch precursor dihydropyridines **3** are utilised, oxidation no doubt being achieved by the iminium salt acting as a hydride abstractor (Scheme 2).

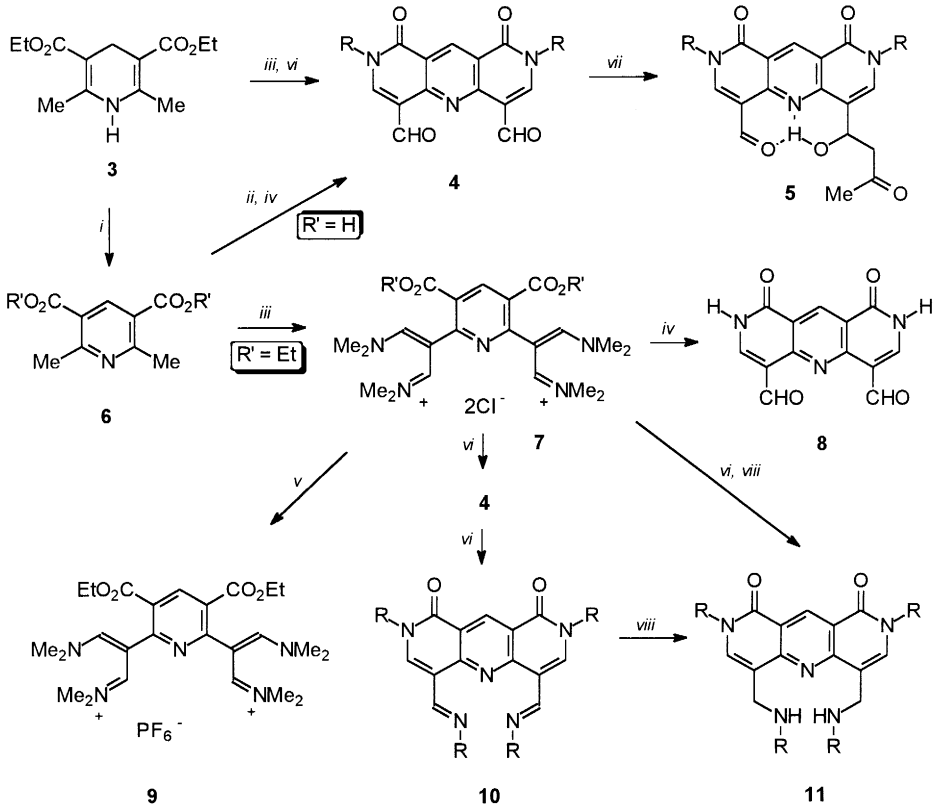
Table 1
DOTTADs (**4**) derived from pyridines **6** (R′=H)

Entry	formamide (mM)	Product (**4**)	yield (%)	mp (°C)
1	DMF (60)	R = Me	88	339
2	Et_2NCHO (42)	R = Et	46	282
3	*i*-Pr_2NCHO (42)	R = *i*-Pr	0	-
4	$(CH_2{=}CHCH_2)_2$ NCHO (60)	R = $-CH_2CH{=}CH_2$	76	235
5	$(CH_2)_4NCHO$ (60)	R = $-(CH_2)_4Cl$	85	216
6	$(CH_2)_5NCHO$ (42)	R = $-(CH_2)_5Cl$	~ 100	182

Table 2
DOTTADs (**4**) and related systems derived from pyridines **6** (R′=Et)

Entry	R =	Product	yield (%)	mp (°C)
1	-	**8**	90	> 310
2	-	**9**	100	>310
3	Me-	**10a**	73	247-8
4	Et-	**10b**	62	280
5	n-Bu -	**10c**	58	119-20
6	$CH_2{=}CHCH_2$ -	**4d**	80	235
7	$PhCH_2$-	**10e**	73	199
8	(S)-PhCHMe-	**10f**	67	209
9	4-$MeOC_6H_4CH_2$-	**10g**	77	214-5
10	$HOCH_2CH_2$-	**10h**	52	>310

– If the starting material is the Hantzsch acid **6** (R′=H) work-up is best conducted using NH_4OH to avoid metal salt complexation and thus water solubilisation of the product. If, on the other hand the Hantzsch ester **6** (R′=Et) is used as substrate the intermediate tetra-formylated ester **9** (which can be isolated as the PF_6^- salt) does not cyclise but may be induced to do so subsequent to the reaction. Thus, work-up with NH_4OH in this case gives the parent DOTTAD **8** while work-up with a primary amine RNH_2 gives the corresponding DOTTAD **4** bearing the NR substituent or the corresponding imine **10** depending upon work-up method. R can be multivariant, including homochiral functions (Table 2, entry 8 and Table 3).

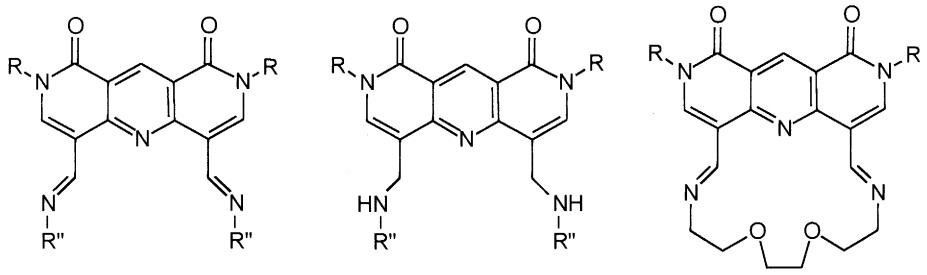


Scheme 2. Reagents and conditions (i) HNO_3; (ii) R_2NCHO, $POCl_3$, 85°C; (iii) DMF, $POCl_3$, 85°C; (iv) NH_4OH, rt; (v) NH_4PF_6; (vi) RNH_2, rt; (vii) acetone; (viii) $NaB(OAc)_3H$, $ClCH_2CH_2Cl$, rt

– If instead of DMF, a cyclic formamide is used (e.g. *N*-formylpyrrolidine, *N*-formylpiperidine etc.) ring-opening of the intermediate occurs to give a DOTTAD bearing an ω-chloroalkyl function on the terminal ring nitrogens (e.g. $(CH_2)_4Cl$ or $(CH_2)_5Cl$ etc). Alternatively, a different formamide (R_2NCHO, e.g. diallylformamide) yields the corresponding *R*-substituted DOTTAD **4** (e.g. R=allyl).
– The aldehyde groups of the DOTTADs are surprisingly untypical in their reaction style. Thus, reduction with $NaBH_4$ is surprisingly messy, while attempts to reduce the readily made corresponding imines was also problematic. After much experimentation with different methods we have found that sodium triacetoxyborohydride is the most effective reductant for the latter process (the aldehyde and amine mixture can be utilised). In this way, various homochiral imine **10**/**12** and amine **11**/**13** derivatives have been generated. The imine or amine NR′′ group can be different from the ring NR substituent (Table 3). Merely dissolving a pure DOTTAD in acetone yields the mono-aldol adduct **5** rapidly, but so far attempts to make the bis-aldol adduct have failed.
– ‘Crowned’ DOTTADs **14** are easily accessible by use of an appropriate α,ω-diaminoether precursor under high dilution.
– The substituent on the ring nitrogen can be manipulated to confer useful solubility or to create a ‘handle’ for further manipulation of these crystalline ligands (Table 3).

It is evident that these interesting systems have considerable potential for useful ligand action and thus also for metal-catalysed reactions, particularly for homochiral catalysis. For example, the imines **10** are excellent ligands for copper(II) salts. This aspect is now under active investigation.

Table 3



12 13 14

Entry	Starting material **4** R =	Product	Method	Yield (%)
1	Me	**12** R" = Ph	A	58
2	$Cl(CH_2)_4$-	**12** R" = Ph	A	85
3	$Cl(CH_2)_4$-	**12** R" = 4-$MeOC_6H_4$	A	95
4	$Cl(CH_2)_4$-	**12** R" = 3-$NO_2C_6H_4$	A	80
5	$Cl(CH_2)_4$-	**12** R" = (S)-Ph-CHMe-	A	93
6	$Cl(CH_2)_4$-	**13** R" = (R,S)-Ph-CH(OH)CHMe-	B	78
7	CH_2=CH-CH_2-	**13** R" = (R,S)-Ph-CH(OH)CHMe-	B	69
8	CH_2=CH-CH_2-	**12** R" = Ph	A	70
9	CH_2=CH-CH_2-	**12** R" = 4-MeC_6H_4	A	75
10	$Cl(CH_2)_4$-	**14**	C	45
11	CH_2=CH-CH_2-	**14**	C	51

Method A: R"NH_2, EtOAc, reflux; Method B: R"NH_2, $NaB(OAc)_3H$, $ClCH_2CH_2Cl$, r.t.;
Method C: $NH_2CH_2CH_2OCH_2CH_2OCH_2CH_2NH_2$, CH_2Cl_2, high dilution;

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References

1. Meth-Cohn, O.; Taljaard, H. C. *Tetrahedron Lett.* **1983**, *24*, 4607–4610. Meth-Cohn, O. *S. Afr. J. Chem.* **1987**, *40*, 189–191.
2. *General procedure:* $POCl_3$ (9.3 ml) was added dropwise to an *N*-formyldialkylamine (4–6 mM, see Tables 1 and 2) with efficient stirring and external ice cooling. To this solution was added the 2,6-dimethylpyridine-3,5-dicarboxylic acid or ester (10 mM) and after one minute stirring the mixture was heated at 80–85°C for 12 h (acid) or 48 h (ester), during which it became red. Most of the $POCl_3$ was removed in vacuo and ice/water added, followed by concentrated NH_4OH or the required amine until basic. After 30 min stirring the tan coloured precipitate was filtered, washed well with water and dried and recrystallised from either ethyl acetate, acetonitrile or acetic acid to give generally a pale yellow crystalline solid.