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Synthetic Applications of Umpoled Vilsmeier Reagents - A New Simple One-Pot Route to Isatins from Formanilides

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Abstract: When *N*-substituted formanilides are treated briefly and sequentially with oxalyl chloride, Hünig's base, and bromine, isatins are rapidly formed, many in good yields. The reaction involves deprotonation of the Vilsmeier reagent, dimerisation of the carbene thus formed and electrophilic cyclisation of the dimer by bromonium ion action followed by aqueous hydrolysis.
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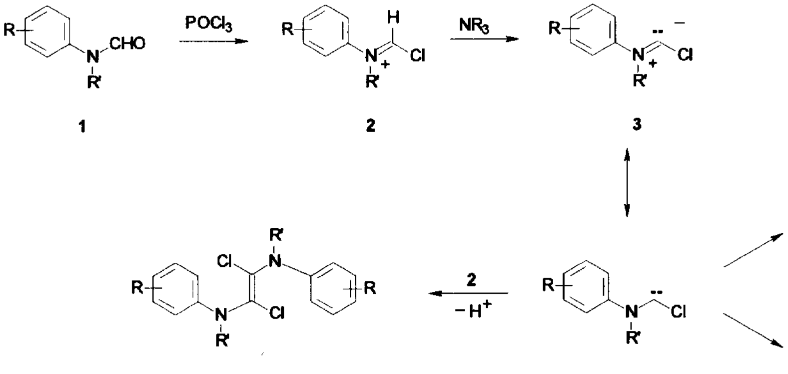
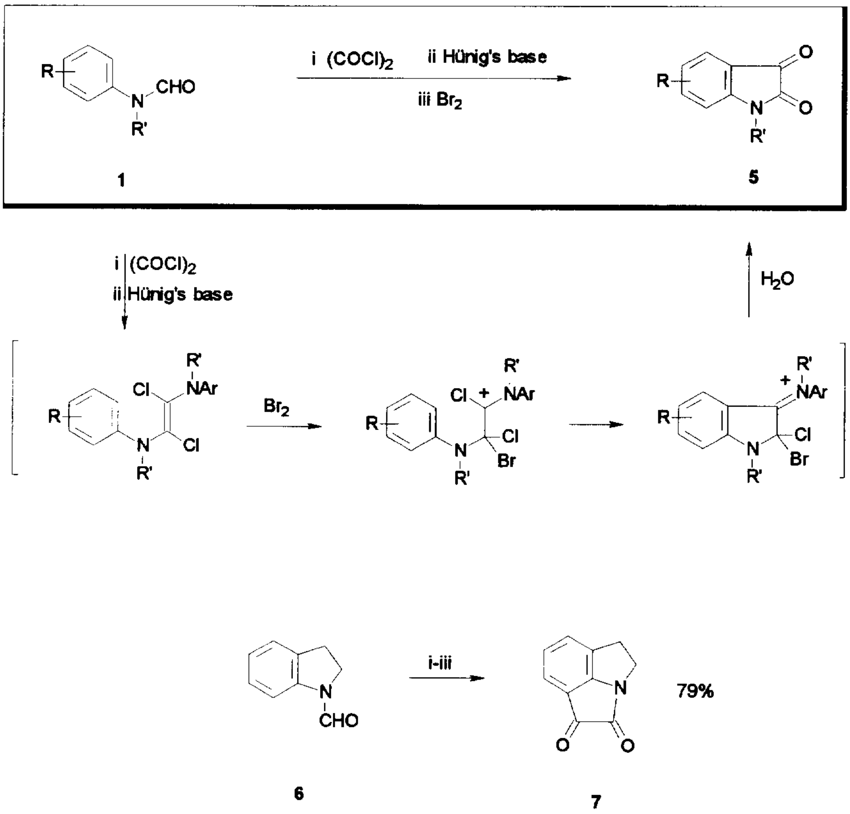
We recently disclosed[1] the unexpected formation of nucleophilic carbenes **3** from Vilsmeier reagents **2** by the action of tertiary nitrogen bases in $POCl_3$ (Scheme 1) - a process which in effect 'umpoles' the Vilsmeier reagent. The products formed from the carbene depend upon conditions but include the dimers **4** and on occasions, minor amounts of isatins. In an overlooked but seminal paper Böhme and Sutoyo[2] observed that



Scheme 1

dimethylformamide and *N*-methylformanilide undergo a similar formation of dimer by sequential action of oxalyl chloride in THF followed by treatment with Hünig's base. They also noted a number of reactions of the unstable DMF-derived dimer. Even the arylamino-dimers **4** have a limited shelf-life and in trying to unravel the origin of the formation of isatins we found that the dimers reacted with electrophiles such as bromine to yield isatins. In order to obviate the dimer instability and as part of an ongoing programme to define the synthetic application of 'umpoled' Vilsmeier reagents, this useful reaction has now been developed into a simple, brief and efficient one-pot isatin synthesis from formanilides (Scheme 2, Table). The reaction appears to be quite general for various ring substituents. The reaction proceeds even with electron-withdrawing substituents present such as a nitro-group. It is clear that some optimisation is necessary for individual cases since we find, for example, that the reaction with bromine gives optimal yields in one case (*cf* expts. 6-8) after 2h reaction



Scheme 2

while isolated dimer 4 (R = 2-Cl) gives better yields than in the one-pot standard procedure. The anti-inflammatory isatin[3] 7 is readily prepared from *N*-formylindoline 6 in high yield.

Isatins are important intermediates (e.g. in the highly useful Pfitzinger quinoline synthesis[4]), are found in nature[5], and are topical, having key roles in plant[6], animal[7],and human[8] metabolism, being implicated in, for example, bulimia nervosa. To our knowledge other useful routes to isatins (e.g. the Sandmeyer method[9] or the related cyclisation of oxalylanilides[10]; see also the recent method of Hewawasam and Meanwell whereby *o*-lithiated protected anilines are reacted with oxalate esters, deprotected and cyclised[11]) are moderate yielding methods involving at least 2-steps.

A typical procedure is as follows:

The *N*-substituted formanilide (10mmol) and oxalyl chloride (10mmol) are mixed with stirring at ambient under nitrogen until gas evolution ceases (~30min.). Dry THF (10mL) is added and the suspension is cooled in an ice-bath while Hünig's base (10mmol) is added slowly dropwise over 10-15min. The flask is then heated to 35°C for 1h, again cooled in an ice-bath and bromine (5mmol) in chloroform (2mL) is added dropwise yielding a purple solution. Water (50mL) is added causing the colour to change to orange and the solution extracted with ether, washed with 2M hydrochloric acid (3x 25mL), then water and dried ($MgSO_4$) and the solvent removed to yield product of surprising purity, further easily purified by crystallisation or flash chromatography.

TABLE

Formanilide (1) Expt	R =	Electrophile	Yield of isatin (5) and comments
1	H	Br_2	62%
2	4-F	"	62
3	4-F	TFA	48 after 90min at 50°C
4	4-Br	Br_2	71
5	4-Cl	"	65
6	4-Cl	Br_2 and 2h at RT	78
7	4-Cl	Br_2 and 24h at RT	70
8	4-Cl	TFA	45 after 90min at 50°C
9	2-Cl	Br_2	20
10	2-Cl	"	40 from isolated dimer
11	3-Cl	"	11
12	4-Cl	TFA	45 after 90min at 50°C
13	4-Me	Br_2	58
14	4-OMe	"	66
15	4-NO_2	"	34

Alternative electrophiles such as proton (TFA), $SOCl_2$, SO_2Cl_2, benzenediazonium hexafluorophosphate or BF_3.etherate give isatins in reduced yields.

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