New versatile approach to α-hydrazonoesters and amino acid derivatives through a modified Japp–Klingemann reaction

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Addition of diazonium tetrafluoroborates to an acyl chloride pyridine mixture affords hydrazonoacid derivatives in smooth conditions; this new Japp–Klingemann reaction emphasizes the synthetic potential of electrophilic addition to ketenes.

Hydrazones are associated with a wealth of well-known reactions such as the Wolff–Kishner,[1] the Shapiro[2] reactions or the Eschenmoser rearrangement.[3] Numerous asymmetric catalytic reductions of compounds with carbon–nitrogen double bonds have been carried out,[4] among these α-hydrazonoesters have shown a great potential as enantiopure amino acid precursors.[5] The importance of these reductions has given us the impetus to search for new selective access to these valuable intermediates.

α-Hydrazonoesters are usually prepared by a Japp–Klingemann[6] reaction between an arenediazonium salt and a malonic acid derivative. It is a two step process involving coupling of the active methylene compounds followed by a final decarboxylation. Simple acid derivatives are not acidic enough and their use as starting materials for Japp–Klingemann reactions often requires preliminary carboethoxylation of the compound. Recently Sakakura *et al.*[7] described a direct preparation of α-hydrazonoester from ester *via* ketene silyl ketals but their reaction requires the use of a strong base (*e.g.* LDA) which may not be compatible with sensitive substrates.

In connection with our previous study on the trifluoroacetic anhydride additions to ketenes,[8] we believed that α-hydrazonoesters could be prepared in one step directly from the acid chloride. This reaction would involve electrophilic diazonium salt attack on the corresponding ketene generated under weak base treatment. Electrophilic attacks on ketenes are well precedented[9] but this reactivity has been poorly explored in comparison to nucleophilic attack. Indeed, by adding diazonium salt **2b** to a mixture of acid chloride **1a** and pyridine, we observed the formation of α-hydrazonoester **3b** with a yield of 63% (Scheme 1, Table 1).

The interest of this method lies in the generation of the ketene with a large excess of pyridine (3 equiv.) which avoids ketene dimerisation by forming zwitterion **A**. The latter can be attacked by the diazonium giving the azocompound **B** and **C** through further deprotonation (Scheme 2); ethanolysis of **C** finally gives hydrazonoesters **3**.

The reaction is performed at room temperature in dichloromethane using 3 equiv. of pyridine and 1.1 equiv. of diazonium salt (added 10 min after the ketene–pyridine adduct formation).
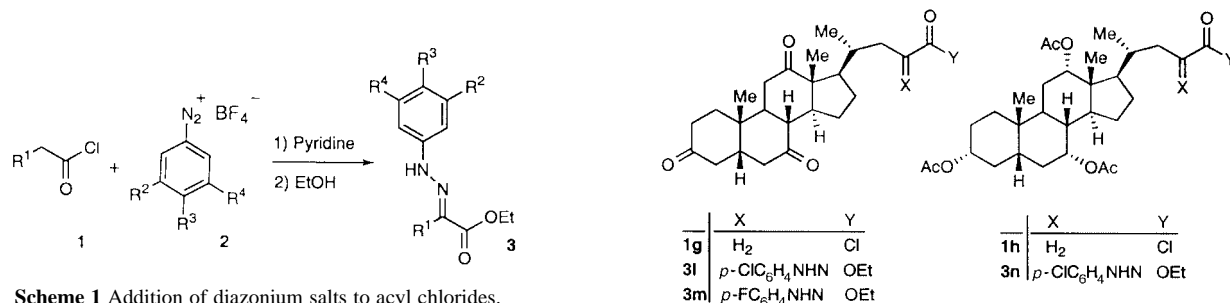
Table 1 Formation of hydrazones **3** from diazonium salts **2**

Chloride **1**	Diazonium **2**	Product **3**[a]	Yield (%)
1a	**2a**	**3a**	33
1a	**2b**	**3b**	63
1a	**2c**	**3c**	66
1a	**2d**	**3d**	56
1a	**2e**	**3e**	55.5
1b	**2b**	**3f**	78
1b	**2c**	**3g**	67
1c	**2b**	**3h**	83
1d	**2b**	**3i**	40
1e	**2b**	**3j**	65
1f	**2b**	**3k**	41
1g	**2b**	**3l**[b]	63
1g	**2c**	**3m**[b]	55
1h	**2c**	**3n**[b]	57

[a] To a dichloromethane solution of acid chloride (0.25 M) was added pyridine (3 equiv.) and after 10 min the diazonium salt **2** (1.1 equiv.). [b] Same procedure but with 0.12 M concentration.

Scheme 1 Addition of diazonium salts to acyl chlorides.
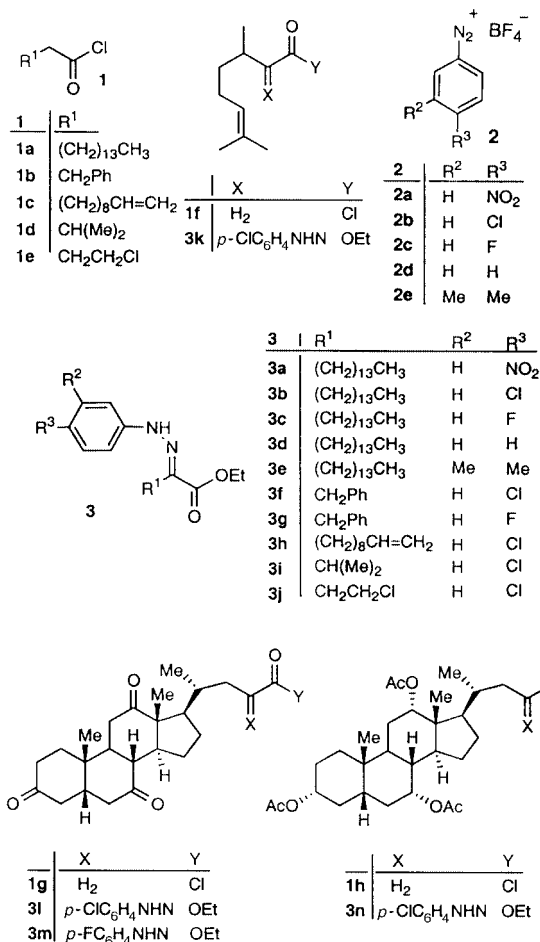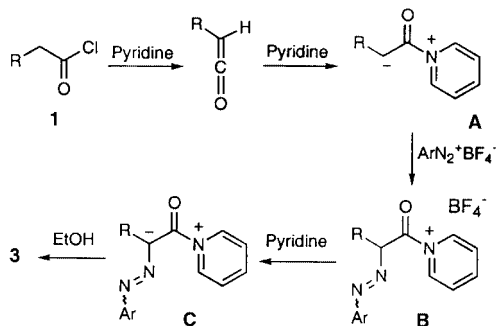
Scheme 2 Possible intermediates in α-hydrazono ester formation.
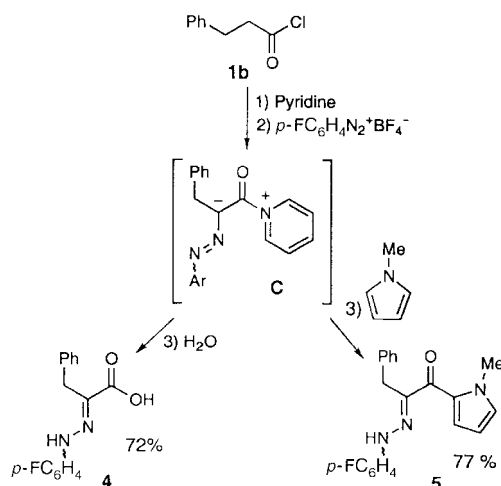
Scheme 3 Acid chloride–diazonium manifold.

The reaction is best carried out at 0.25 M concentration except for steroids **3n**, **3o**, **3p** for which it was reduced to 0.12 M. The

results, reported in Table 1, show that moderate to good yields were obtained for most diazonium salts tested and that this new method is compatible with various sensitive functions such as esters and ketones (**3n**, **3o**, **3p**).

The strength of this approach is further underlined by the manifold provided by the final treatment: when ethanolysis gives esters, hydrolysis can form directly free α-hydrazonoacids whereas addition of *N*-methylpyrrole in the mixture forms pyrrole substituted derivatives in a Friedel–Craft acylation type reaction (Scheme 3).

The potential of this new reaction as well as other additions of electrophiles to ketenes are still under investigation in our research group.

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Notes and references

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