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Development and Optimisation of an Unsymmetrical Hantzsch Reaction for Plant-Scale Manufacture

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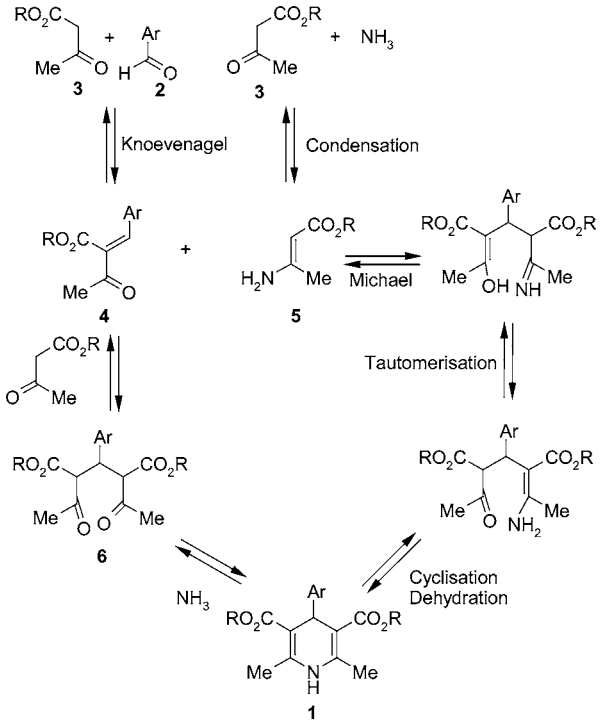
Abstract:

(*S*)-3-(5-Oxo-2-(trifluoromethyl)-1,4,5,6,7,8-hexahydroquinolin-4-yl)benzonitrile is a potassium-channel opener developed for the treatment of urinary urge incontinence. The key step in the synthesis is an unsymmetrical Hantzsch reaction to give a 2-hydroxy-1,2,3,4-tetrahydropyridine. In our study the order of addition of reagents was found to be critical in the optimisation of the yield and the control of impurity levels in this reaction. The yield and the relative charges of the reagents were further optimised by the use of factorial experimental design. The chemistry has been scaled up to plant scale to produce multikilogram amounts of the Hantzsch product in close to 60% yield.

Introduction

The first synthesis of a 1,4-dihydropyridine (1,4-DHP) was reported by Arthur Hantzsch in 1882[1] and is still the most common method for the preparation of these compounds. The classic Hantzsch reaction involves the combination of 1 equivalent of an aromatic aldehyde, 2 equivalents of a β-keto-ester and 1 equivalent of ammonia in an alcoholic solvent at reflux to give the 1,4-DHP, commonly known as a Hantzsch Ester (**1**) (Scheme 1).[2] The reaction can formally be thought of as proceeding in several discrete steps (Scheme 1); Knoevenagel condensation of the aldehyde (**2**) with one molecule of the β-keto-ester (**3**) to give the Knoevenagel product (**4**), condensation of the other equivalent of the β-keto-ester (**3**) with ammonia to give an enamine (**5**), Michael reaction of the enamine (**5**) and Knoevenagel product (**4**), followed by cyclisation and then dehydration (Scheme 1). Evidence for the mechanism is largely based on the fact that the Knoevenagel products (**4**), enamines (**5**), and 1,5-diketones (**6**) are all effective starting materials for the preparation of 1,4-DHPs.[3] The exact sequence of intermediates is difficult to determine since many of the "stages" are, in fact, equilibria. In the last century or so a large variety of substrates has been shown to successfully undergo this reaction, giving rise to substitution at each position on the dihydropyridine ring;[4] the enamine (**5**) and Knoevenagel products (**3**) can also be assembled using different β-keto-esters and combined to give unsymmetrical Hantzsch esters (**1**).[5]

Scheme 1. **Possible intermediates in the Hanzsch reaction to form 1,4-DHPs**



Compounds containing the 1,4-DHP motif have proved to be successful therapeutic agents against cardiovascular targets.[6] For example, nifedipine (**7**), a first-generation drug for the treatment of hypertension, has symmetrical substitution on its DHP ring and is achiral. Later generations of 1,4-DHP compounds contain unsymmetrical substitution and are therefore chiral at the C4-position (Figure 1). All of these drugs are closely structurally related, varying only in the substitution on the aromatic ring and the C-3 ester groups (and all except amlodipine have Y = Me[6]). The Hantzsch reaction offers an efficient route to symmetrical 1,4-DHP compounds, since all the carbon atoms in the product can be assembled in one step from relatively simple starting materials. A survey of the literature has shown that a Hantzsch reaction is also often used to construct unsymmetrical products, but that the enamine intermediate is typically prepared *in a separate vessel* before combining with

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(1) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1−82.
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(3) Li, J.-J.; Corey, E. J. *Name Reactions in Hetercyclic Chemistry;* Wiley: New Jersey, 2005, and references therein.
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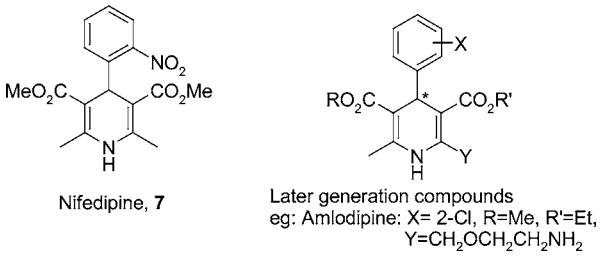
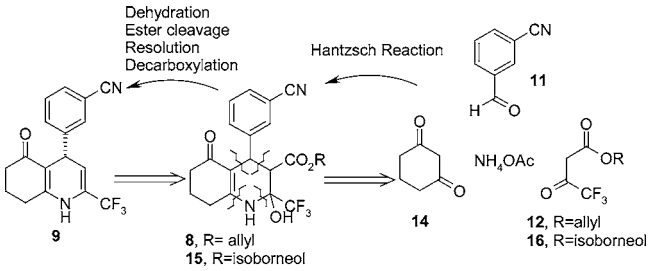


Figure 1. **Therapeutic agents containing the 1,4-DHP motif.**

Scheme 2. **Retrosynthesis of the target drug molecule (9)**



the other components to give the Hantzsch Ester;[7] presumably this is to avoid formation of the symmetrical byproducts.

This paper describes the development of a *one-pot* unsymmetrical Hantzsch reaction that has been successfully scaled up to produce over 1 tonne of Hantzsch product (**8**) for drug development (Scheme 2). Formation of the symmetrical byproducts was successfully overcome by careful control of the order of addition of the reagents, which also led to an improved mechanistic understanding of the reaction.

Background

Initial retrosynthesis of our target drug molecule (**9**) showed the Hantzsch synthesis to be an attractive reaction to investigate (Scheme 2). Since the Hantzsch reaction does not control the stereochemistry at C4, the potential output from this synthetic route is limited by the fact that it involves a classical resolution. To overcome this, an alternative, asymmetric synthesis of **9** has been developed and reported.[8] However, in the meantime, the Hantzsch route in Scheme 2 has proved to be robust on a plant scale, giving an overall yield of 16.3%, which compares favourably with the asymmetric route.

Of particular relevance to **8**, it has been demonstrated[9] that Hantzsch reactions using trifluoromethyl acetoacetate give 2-hydroxy-1,2,3,4-tetrahydropyridines rather than 1,4-DHPs directly, and therefore we expected our synthesis to require a separate dehydration step.

There are two potential symmetrical Hantzsch esters which can also form from these reagents, the diester impurity (**10**), formed from the reaction of 1 molecule of 3-cyanobenzaldehyde (**11**) and 2 molecules of the ester (**12**), and the tricyclic impurity (**13**), formed from 1 molecule of 3-cyanobenzaldehyde (**11**) reacting with 2 molecules of the

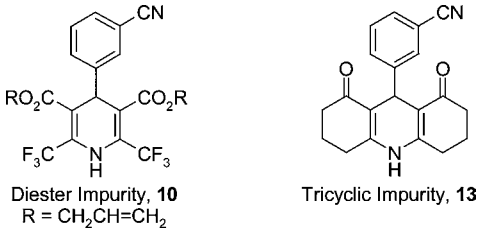


Figure 2. **Possible symmetrical Hantzsch ester products.**

dione (**14**) (Figure 2). A viable plant-scale process would need to control the levels of these and any other impurities.

Discussion

The procedure used for gram-scale synthesis of **8** was based on literature precedent and involved the addition of all four reagents (R = isoborneol, Scheme 2) to the reaction flask followed by the solvent (EtOH). The reaction was heated to reflux for 8 h and then seeded to induce crystallisation of the tricyclic impurity (**13**). The reaction mixture was screened to remove tricyclic impurity (**13**) and then concentrated to half its volume to allow isolation of the first crop of product (**8**) by filtration. Evaporation of the liquors to dryness and trituration of the residue with diethyl ether allowed isolation of a further crop of product (**8**); a third crop was isolated by column chromatography to give a total yield of ca. 60%.

The issues relevant to plant-scale manufacture using the initial gram-scale process were:

(i) the difficulty of cleaving the isoborneol ester (**15**) without causing decarboxylation to racemic final product (**9**)

(ii) the level of tricyclic impurity (**13**) (typically 15−30%) and diester impurity (**10**) (typically 2−4%) at the end of the reaction

(iii) possible hazard issues arising from the "all-in" nature of the reaction

(iv) isolation of the product by evaporation to dryness and using chromatography

(v) the need for three isolations (one of which suffers from a slow filtration rate)

(vi) low output of the process (the reaction was carried out in 40 relative volumes)

Early in development, the isoborneol ester (**16**) was replaced by the analogous allyl ester derivative (**12**), having demonstrated that the allyl group could be cleaved without any decarboxylation using catalytic amounts of Wilkinson's catalyst[10] or another suitable metal.

A screen of alternative solvents showed none that offered any benefit over EtOH, so this remained the solvent for the reaction. An extensive study of the order of addition of the components of the reaction was then undertaken to control the levels of the diester (**10**) and tricyclic (**13**) impurities (Figure 2).

In general, adding two or more reagents to another already at reflux gave higher ratios of these impurities. It was therefore decided to combine all the reagents at ambient temperature before heating to increase the overall rate of reaction to give the product (**8**). Examination of the original

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Table 1. **Comparison of orders of addition of reagents**

entry	second reagent	conditions	third reagent	fourth reagent	result
1	allyl ester (**12**)	RT	−	−	no reaction
2	ammonium acetate	RT	allyl ester (**12**)	−	diester pyran (**19**)
3	ammonium acetate	heat	allyl ester (**12**)	−	diester impurity (**10**)
4	ammonium acetate	RT	allyl ester (**12**) and dione (**14**)	−	pyran intermediate (**17**)
5	ammonium acetate	RT	allyl ester (**12**)	dione (**14**)	low yield of product (**8**)
6	dione (**14**)	RT	−	−	tricyclic pyran (**18**)
7	dione (**14**)	reflux	ammonium acetate	−	tricyclic impurity (**13**)
8	ammonium acetate	20−40 °C	dione (**14**)	−	intermediate (**21**) then tricyclic pyran (**18**)
9	ammonium acetate	60 °C	dione (**14**)	allyl ester (**12**)	pyran intermediate (**17**) then product (**8**)

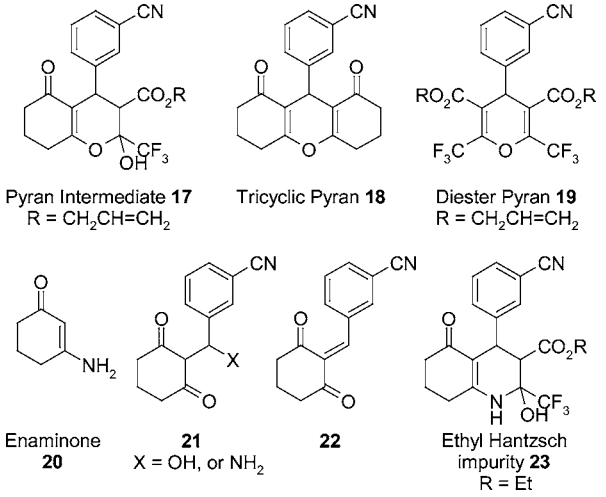


Figure 3. **Impurities and Intermediates.**

process showed that an intermediate, later identified as the pyran intermediate (**17**) (Figure 3), precipitated during the warming of the reaction mixture and was subsequently converted to the product (**8**) during the hold at reflux. The formation of the pyran intermediate (**17**) requires that the dione (**14**), 3-cyanobenzaldehyde (**11**), and the allyl ester (**12**) react together. However, a one-pot reaction of these three reagents without ammonium acetate did not give **17** but formed mainly the tricyclic pyran (**18**) and diester pyran (**19**) instead. This result suggests that ammonium acetate is involved in the formation of the pyran intermediate (**17**), as well as in the conversion of the pyran intermediate (**17**) to the product (**8**).

Adding the other reagents to either the dione (**14**) or the allyl ester (**12**) in ethanol at either reflux or ambient temperature led to higher proportions of the tricyclic impurity (**13**) and the diester impurity (**10**), respectively. Attempted preformation of the enaminone (**20**) (Figure 3) followed by addition of the other reagents also resulted in a poor reaction profile.

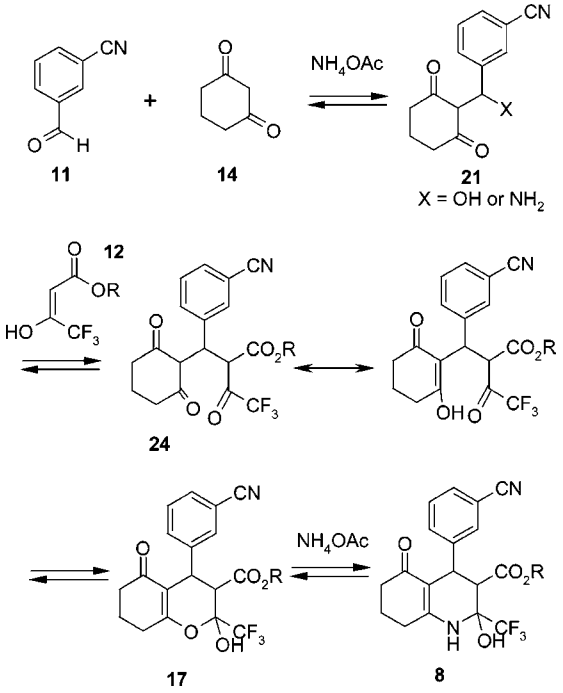
These results led to the decision to start with 3-cyanobenzaldehyde (**11**) in ethanol and add the other reagents to it in various orders, either neat or as a solution in ethanol, and at various temperatures. Table 1 shows the results of these experiments. Allyl ester (**12**) does not react with 3-cyanobenzaldehyde (**11**) at ambient temperature (entry 1), although combining 3-cyanobenzaldehyde (**11**) with ammonium actetate and then adding allyl ester (**12**) gives the diester pyran (**19**) (Figure 3 and entry 2). This adds credance to our supposition that the ammonium acetate is involved in the early stages of the reaction, although the ammonia does not become irreversibly incorporated until a later stage. This mixture of 3-cyanobenzaldehyde (**11**), ammonium acetate, and allyl ester (**12**) gives the diester impurity (**10**) on heating (entry 3).

Adding a mixture of allyl ester (**12**) and dione (**14**) to a mixture of 3-cyanobenzaldehyde (**11**) and ammonium acetate gives rapid consumption of dione (**14**), followed by eventual formation of pyran intermediate (**17**) (entry 4). This implies that the dione (**14**) reacts more readily than allyl ester (**12**) with the mixture of 3-cyanobenzaldehyde (**11**) and ammonium acetate. Following this, it was thought that separating the addition of allyl ester (**12**) and dione (**14**) and adding the allyl ester (**12**) first to a mixture of 3-cyanobenzaldehyde (**11**) and ammonium acetate, followed by dione (**14**), might give the required product (**8**). This proved to be the case but only in low yield (entry 5).

Having shown that adding allyl ester (**12**) at an early stage was not successful, we tried adding dione (**14**) as the second reagent. A mixture of 3-cyanobenzaldehyde (**11**) and dione (**14**) at room temperature (entry 6) gave tricyclic pyran (**18**) (Figure 3). Adding ammonium acetate to this mixture and heating to reflux gave tricyclic impurity (**13**) as expected (entry 7). Comparison of entries 6 and 1 shows that dione (**14**) reacts more readily than allyl ester (**12**) with 3-cyanobenzaldehyde (**11**), as well as with a mixture of 3-cyanobenzaldehyde (**11**) and ammonium acetate. This implies that adding dione (**14**) before allyl ester (**12**) might be a more successful strategy for the reaction.

Consequently, dione (**14**) was added to a mixture of 3-cyanobenzaldehyde (**11**) and ammonium acetate. Heating this mixture to 20−40 °C gives an intermediate which can be detected by HPLC (entry 8). If *no* allyl ester (**12**) is added, this slowly forms the tricyclic pyran (**18**) (entry 8). This leads to the proposal that the intermediate formed between 3-cyanobenzaldehyde (**11**), ammonium acetate, and dione (**14**) could be **21** (X = OH or NH_2, Figure 3), where the ammonium acetate is acting either by forming an imine of 3-cyanobenzyaldehyde (**11**) or simply as an acid catalyst of the reaction. Consistent with either of these structures, the intermediate was found to decompose slowly at room temperature to tricyclic pyran (**18**) and 3-cyanobenzaldehyde (**11**), presumably via elimination to an intermediate such as **22**; this decomposition was faster at elevated temperatures and in polar aprotic solvents such as NMP. If allyl ester (**12**) *is* added to the proposed intermediate (**21**) (entry 9) and the

Scheme 3. **Proposed reaction sequence for the formation of 8 (R = $CH_2CH{=}CH_2$)**



mixture heated to 60 °C, a solid precipitates from the reaction which has been identified as the pyran intermediate (**17**). Further heating eventually gives the required Hantzsch product (**8**).

The enaminone (**20**) (Figure 3) has never been detected by HPLC during a reaction and therefore is not an intermediate in the reaction, is a very reactive intermediate, or is perhaps not stable under the HPLC conditions used. Another impurity, the ethyl Hantzsch impurity (**23**) (Figure 3), has been traced back to contamination of the allyl ester (**12**) with ethyl trifluoroacetoacetate, from which it is manufactured by transesterification. The level of the ethyl Hantzsch impurity (**23**) is controlled by setting strict limits on the level of ethyl trifluoroacetoacetate allowed in the allyl ester starting material (**12**).

As a result of these experiments the reaction sequence shown in Scheme 3 was proposed, and the order of addition of [(3-cyanobenzaldehyde (**11**) + ammonium acetate) + dione (**14**)] + allyl ester (**12**) was adopted, followed by heating to complete the reaction. Hazard assessments showed that the balance of reaction rates with energy output was such that this "all-in" approach would not cause concern on scale-up.

Isolation of the product (**8**) was achieved by removal of some solvent by distillation, addition of water to precipitate more of the product, and then cooling and filtering. The product (**8**) is known to decompose slowly at higher temperatures; therefore, in anticipation of longer distillation times during plant-scale manufacture, the distillation was carried out under vacuum so that a lower temperature could be used. Initially the workup was dogged by poor filtration times, but this poor performance was found to be due to small amounts of pyran intermediate (**17**) contaminating the product (**8**). The inclusion of a screen at 60 °C to remove

Table 2. **Effects of increased charges of ammonium acetate**

		HPLC area % after reflux period		
entry	NH_4OAc (equiv)	Hantzsch product (**8**)	pyran intermediate (**17**)	tricyclic impurity (**13**)
1	2.65	49.2	3.3	15.8
2	5.3	54.4	0.5	18.9
3	2 × 2.65	58.5	<0.4	15.1

Table 3. **Factors investigated in statistical experimental design**

	values		
reagent	midpoint	low	high
dione (**14**)	1.0 equiv	0.9 equiv	1.3 equiv
ammonium acetate	2 × 2.65 equiv	2 × 2.5 equiv	2 × 3.5 equiv
allyl ester (**12**)	1.1 equiv	0.9 equiv	1.3 equiv
volume of reaction	25.6 vols	20 vols	35 vols

any unconverted pyran intermediate (**17**) before distillation to remove excess solvent, and controlled cooling and addition of water to crystallise the product, resulted in a marked improvement in the filtration times. The product (**8**) was then slurry washed with water to remove any residual ammonium acetate and then with MTBE, which was found to be the best solvent for removing impurities without dissolving the product.

At this point the outline of a good manufacturing process was established and used to produce 145 kg of **8** on a development plant. However, the yield and impurity profile were subsequently improved still further by optimising the relative charges of the reagents and the concentration of the reaction. In particular, the screening off of pyran intermediate (**17**) represented "wasted" product since this material had essentially undergone the required reaction except for the replacement of an oxygen atom with a nitrogen. The presence of more ammonium acetate might be expected to improved the conversion of pyran intermediate (**17**) to product (**8**). Doubling the initial charge of ammonium acetate from 2.65 to 5.3 equiv decreased the level of pyran intermediate (**17**) seen at end of reaction before isolation (Table 2, entry 2 vs entry 1); including two separate charges of ammonium acetate (one with the 3-cyanobenzaldehyde (**11**) and one after the addition of all other reagents, just before heating to reflux), so that the maximum possible ammonium acetate was present after the addition of all reagents and during the period at reflux, decreased the level of pyran intermediate (**17**) to such a level that the screen was removed in further campaigns (entry 3). These conditions were then used as the baseline conditions for further experiments.

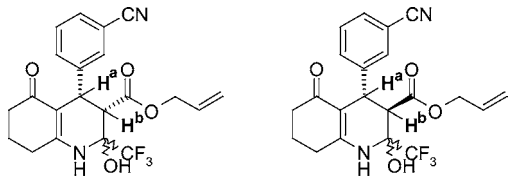
The optimisation of the charges of the reagents and concentration of the reaction was achieved in a time-efficient manner using factorial experimental design. The charge of 3-cyanobenzaldehyde (**11**) was fixed and the equivalents of dione (**14**), ammonium acetate, ethanol, and allyl ester (**12**) were each varied at two levels (Table 3). This led to an FED with four variables at two levels each for which a half-factorial experimental design (eight experiments) was carried

out, with a midpoint reaction before and after the FED experiments. The results showed that the charges of ammonium acetate and allyl ester (**12**) were not critical, but that the charge of dione (**14**) and the concentration had a significant effect on yield at the end of reaction. In fact, these two factors interacted such that the effect of varying the charge of dione (**14**) at high concentration (low volume) has a larger effect than varying the charge of dione (**14**) at low concentration (high volume). Conversely, the reaction is significantly more robust to changes in concentration at high dione (**14**) charges than at low.

These statistical experiments also allowed investigation of the amount of tricyclic impurity (**13**) present at the end of each reaction and showed that the key parameter in this case was the charge of dione (**14**), with higher charges of dione (**14**) giving higher levels of tricyclic impurity (**13**) as might be expected. Since both the yield of the Hantzsch product (**8**) and the tricyclic impurity (**13**) increased with increased charges of dione (**14**), a compromise had to be reached. To control the quality of the Hantzsch product (**8**), it was necessary to limit the potential for contamination by tricyclic impurity (**13**) which required a low charge of dione (**14**). With this parameter fixed, it was therefore necessary to use a relatively high reaction volume (35 volumes relative to 3-cyanobenzyaldehyde (**11**) input) to retain robustness of the system. Thus, the final process represented a sacrifice in throughput to achieve the product of required quality without compromising process robustness. The best conditions established by the FED were therefore 1 equiv of 3-cyanobenzaldyhyde (**11**), 0.9 equiv of dione (**14**), 1.3 equiv of allyl ester (**12**), 2 × 2.5 equiv of ammonium acetate and 35 volumes of solvent. However, since allyl ester (**12**) is a relatively expensive starting material and its charge does not have a strong effect on yield, this charge was later reduced to 1.1equiv for economic reasons. The final process, used for tonne-scale manufacture, is detailed in the Experimental Section. Using this optimised process, typical levels of the diester impurity (**10**) and tricyclic impurity (**13**) at the end of reaction were each <5% by HPLC area, with <0.1% tricyclic impurity (**13**) and no detectable diester (**10**) impurity in the isolated product—a dramatic improvement on the initial conditions (see above).

During the early stages of this work it had been noted that the strength of the product, as calculated by NMR and by HPLC, was markedly different. This was attributed to an unidentified impurity which coeluted with the product on HPLC. To ensure that both NMR and HPLC strengths were comparable and reliable for plant manufacture a new HPLC system was developed.

The new HPLC system showed a new impurity at the end of reaction with a retention time close but not identical to that of the product (**8**). LC/MS showed that the new impurity had the same mass as the product (**8**) so its identity was tentatively assigned as a diastereomer of the product (**8**). This new impurity was almost entirely removed from the product (**8**) during the MTBE wash sequence. Thus, to fully establish its identity, a pure sample was isolated from these MTBE liquors by chromatography.



Diastereoisomer **26** Product **8**

Figure 4. **NMR analysis of diastereomers.**

NMR analysis of this sample confirmed the connectivity of the compound and established it as a diastereomer of the product (**8**). The evidence for this comes from the coupling constants between the two methine protons, H_a and H_b. In the isomer (**26**) (Figure 4), the coupling constant is 6 Hz suggesting one axial and one equatorial proton; whilst in the isolated product (**8**) the coupling constant is 12 Hz, suggesting that both protons are axial.

Further evidence for this diagnosis was obtained from generating theoretical spectra from computer-generated models of the two diastereomers. This modelling was done using the software program *Macromodel*, version 7.0. The two diastereomers were built and minimised, then the coupling constant between the two protons measured using Macromodel's implementation of the electronegativity-modified Karplus equation, which takes into account the electronegativity of attached atoms as well as dihedral angles. The calculated values of the coupling constants for the two diastereomers were 7 and 13 Hz respectively, which fits very well with those measured from the NMR spectrum, as well as with published results.[9]

The identification of the diastereomer is interesting because it means that this reaction exhibits simple diastereoselectivity: the diastereomers with both large groups (3-cyanobenzyl- and allyl ester) equatorial are formed in preference to the diastereomers which have one large group axial. In a classical Hantzsch reaction, dehydration to the DHP would result in a racemic mixture. It is only by virtue of the presence of a $-CF_3$ group, in this case, that the dehydration does not occur concurrently with formation of the ring and that the diastereoselectivity is observed. The diastereomer is present at levels around 15% by HPLC area at the end of the reaction. It is currently removed from the product during the slurry wash in MTBE but represents a possibility for improving the yield of the reaction if an alternative solvent for the slurry wash could be found.

Conclusion

A robust, one-pot, plant-scale procedure for an unsymmetrical Hantzsch reaction has been developed and used to manufacture over 1 tonne of Hantzsch product (**8**) in 58% yield and excellent quality. The learning gained should be applicable to other Hantzsch reactions.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Varian Inova 400 MHz spectrometer with chemical shifts given in ppm relative to TMS at $\delta = 0$. The reaction mixtures and products were analysed by reverse phase HPLC on a Hewlett-Packard 1100 according to the following condi-

tions: column, Genesis C18, 150 mm × 4.6 mm i.d., 4 μm particle size; eluent A: water with 0.1% v/v trifluoroacetic acid; eluent B: acetonitrile with 0.1% v/v trifluoroacetic acid; gradient: 40% eluent B for 7.5 min., then increasing to 70% eluent B after 20 min.; flow rate, 1.0 mL/min; wavelength, 230 nm; injection volume, 10 μL, column temperature, 20 °C. HPLC purities were wt % against a standard of known strength as determined by ^{1}H NMR.

In a typical process, 3-cyanobenzaldehyde (**11**, 1 equiv) and ammonium acetate (2.5 equiv) are slurried together in ethanol (18 rel vols). A solution of dione (**14**, 0.9 equiv) in ethanol (6 rel vols) is added slowly, followed by allyl ester (**12**, 1.1 equiv) and more ammonium acetate (2.5 equiv) in ethanol (11 rel vols). The mixture is heated to reflux for 3.5 h, and then excess ethanol is removed by distillation under vacuum until 18 rel vols remains. Water (24 rel vols) is added to precipitate the product, which is isolated by filtration and washed with water (6 rel vols) and MTBE (6 rel vols, twice). ^{1}H NMR (400 MHz, DMSO) δ 8.09 (s, 1H), 7.56 (dd, J = 5.9, 1.3 Hz, 1H), 7.47 (s, 1H), 7.44−7.33 (m, 2H), 7.26 (s, 1H), 5.55 (dq, J = 22.6, 5.3 Hz, 1H), 5.01 (dd, J = 10.5, 1.3 Hz, 1H), 4.90 (dd, J = 17.4, 1.5 Hz, 1H), 4.31 (ddd, J = 52.9, 13.6, 5.4 Hz, 2H), 3.98 (d, J = 12.0 Hz, 1H), 2.79 (d, J = 12.0 Hz, 1H), 2.65−2.54 (m, 1H), 2.33 (dd, J = 24.3, 6.9 Hz, 1H), 2.11−2.00 (m, 2H), 1.94−1.77 (m, 2H).

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