Tetrahedron Letters 53 (2012) 3056–3060

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 2,3-dicarbonylated pyrroles and furans via the three-component Hantzsch reaction

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ARTICLE INFO

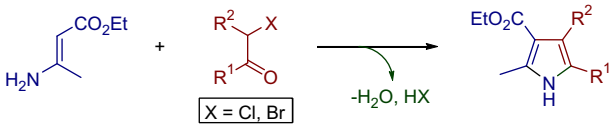
Article history:
Received 6 March 2012
Revised 30 March 2012
Accepted 4 April 2012
Available online 12 April 2012

Keywords:
Hantzsch
Pyrrole
Three-component
Heterocycle

ABSTRACT

Pyrroles containing a 2,3-dicarbonyl substitution pattern are synthesized in one step via a three-component Hantzsch procedure. The normally difficult-to-access substrates are readily obtained in short reaction times and in moderate to good yields, giving pharmaceutically attractive products containing multiple handles for further elaboration.

Pyrroles are an important class of simple heterocycles, being found in a broad range of natural products[1] and displaying a wide spectrum of pharmacological activity.[2] The pyrrole nucleus also occupies a central role in nature, being a structural component of both haem and chlorophyll, as well as finding use in materials science.[3] As such, a number of synthetic methods have been reported for the synthesis of both undecorated, and polysubstituted pyrroles.[4] One of the oldest is the Hantzsch procedure, which involves the condensation of a β-enaminone and an α-halocarbonyl (Scheme 1).[5] The enaminone can be used directly (commonly referred to as a two-component Hantzsch procedure), or can be formed in situ from a ketone and primary amine (three-component). Despite its potential to introduce molecular complexity in a single condensation step, the Hantzsch procedure has not been used widely in the literature. Common problems include poor yields and self-condensation reactions, leading to byproducts and complex reaction mixtures. As such, other procedures such as the Paal–Knorr synthesis are often preferred.[6] However, some studies to widen the scope of the Hantzsch procedure have been reported, such as the use of solid supports[7] and supramolecular catalysis.[8]



Scheme 1. Classical two-component Hantzsch procedure.

During the course of our studies, we required 2-formylpyrrole-3-carbonitrile (**1**) and ethyl 2-formylpyrrole-3-carboxylate (**2**), and derivatives thereof. We were surprised to find that both were poorly precedent in the literature, despite their simplicity and potential use as synthetic building blocks. Although some routes are disclosed for the synthesis of unsubstituted pyrroles bearing 2,3-carbonyl groups,[9] they are typically long and/or limited in scope. In fact, in a recent review on the challenges of synthesizing highly functionalized pyrroles, only one example was given with a substitution pattern similar to **1** and **2**.[10] To the best of our knowledge, only a single report on the synthesis of nitrile **1** is described in the literature, via photochemical pyrolysis of pyridine N-oxides.[11] Requiring a more general route allowing for substitution at the 4- and 5-positions, we initially began by looking to install the aldehyde moiety into a pre-formed pyrrole. Aldehydes (incorporated for example by Vilsmeier–Haack formylation) provide an incredibly versatile platform to access electron-rich heteroaromatic rings via traditional ring synthesis/condensation reactions. However, in the case of ethyl pyrrole-3-carboxylate, primarily the 5-formyl compound is formed (Scheme 2). Oxidation of the known ethyl 2-methylpyrrole-3-carboxylate (**3**) with CAN[12] was also attempted, but in our hands it failed to give any of the desired aldehyde. There are reports that methyl groups at the 2-position of pyrroles can be oxidized by chlorination with sulfuryl chloride,[13] followed by hydrolysis to the aldehyde. However when this was attempted on **3**, a mixture of products were obtained which included products of over-chlorination of the methyl and chlorination of the pyrrole CH positions (Scheme 2).

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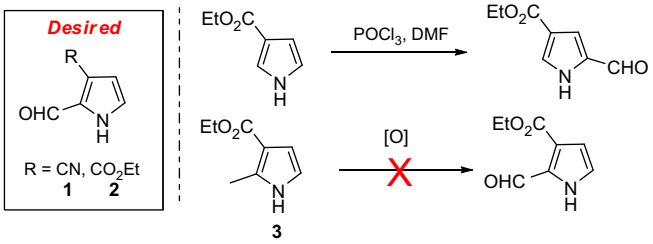
http://dx.doi.org/10.1016/j.tetlet.2012.04.022



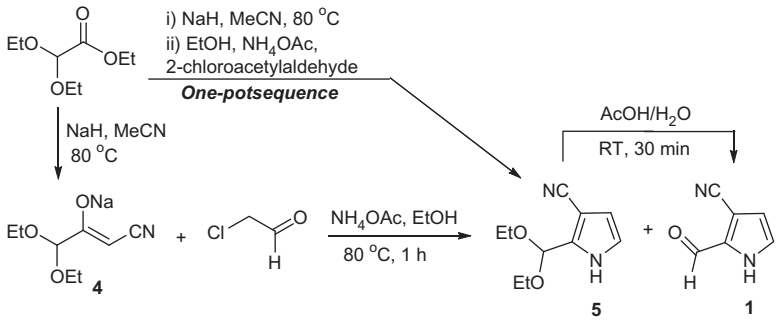
Scheme 2. Failed routes towards **1** and **2**.

Observing that ethyl 2-methylpyrrole-3-carboxylate (**3**) can be synthesized in moderate yields by the Hantzsch reaction of chloroacetylaldehyde and ethyl 3-oxobutanoate, we considered the use of the Hantzsch procedure to access the desired compounds by replacing the methyl with a masked aldehyde moiety. In order to test this hypothesis, we synthesized 4,4-diethoxy-3-oxobutanenitrile from ethyl 2,2-diethoxyacetate and acetonitrile with sodium hydride. We found it to be unstable and difficult to isolate in its protonated form however, which was in agreement with the literature reports for this compound.[14] In order to address the stability issue of 4,4-diethoxy-3-oxobutanenitrile, it was isolated and used directly from the reaction mixture as the sodium salt **4** (after purification by trituration). Treatment of **4** with chloroacetylaldehyde and ammonium hydroxide at room temperature (as per the synthesis of **3**) resulted in a sluggish reaction. Heating **4** with ammonium acetate in ethanol gave rapid conversion into two new products. LC–MS analysis suggested these were primarily the pyrrole-acetal **5**, and a small amount of the desired product **1** (Scheme 3). As the acetal protected product showed a propensity towards hydrolysis even during the condensation reaction, the crude reaction mixture was fully hydrolysed to the desired product by in situ addition of acetic acid/water to give **1** in an acceptable 51% yield. It was in fact possible to access aldehyde **1** in similar yield directly from acetonitrile and ethyl 2,2-diethoxyacetate in a one-pot sequence by telescoping formation of intermediate **4** with the Hantzsch procedure. This constitutes a four-component sequential Hantzsch-type reaction, and should be useful in optimization studies and high throughput chemistry.

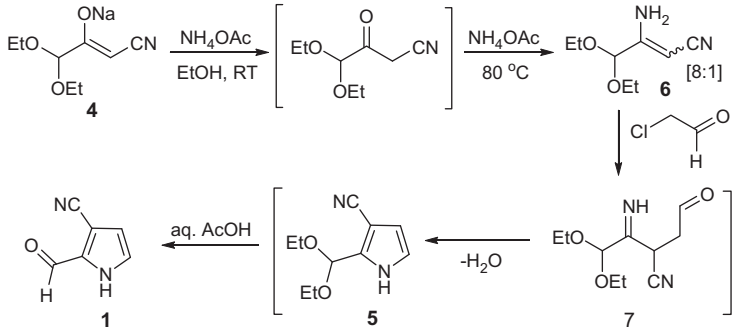
In a typical reaction sequence, enolate **4** was initially stirred with ammonium acetate in ethanol for 5 min at room temperature, which should result in protonation of the enolate **4** to form the unstable acidified keto-nitrile in situ. After 5 min, chloroacetylaldehyde was added and the reaction was warmed to 80 °C. Formation of enamine **6** was expected to occur (this can be isolated directly as an 8:1 ratio of *E*/*Z* enamines when **4** is heated with NH_4OAc in ethanol), followed by alkylation to give an intermediate such as **7**. Intramolecular condensation and aromatization should then occur, followed by hydrolysis of the acetal to give pyrrole **1** (Scheme 4). It should be noted that an alternative mechanism, beginning with initial condensation of enamine **6** through nitrogen onto the aldehyde, followed by intramolecular C–C bond formation with displacement of chloride would also give the same product, and cannot be ruled out.

With this preliminary result in hand, we explored the potential scope of the reaction by reacting **4** with a range of chloro-carbonyl compounds. We also screened selected alkyl amines to see if N-protected pyrroles could be accessed though this method. Pleasingly, the reaction was tolerant of a range of chloroaldehydes and chloroketones as well as alkyl amines, allowing substitution on any position of the pyrrole product (Table 1).

The reaction worked for secondary chloroaldehydes (entry 2) to introduce a methyl into the 4-position of the pyrrole product, and for chloroacetone to introduce a methyl into the 5-position in 55% yield (entry 3). Cyclic halo-ketones (entries 4 and 5) also reacted efficiently to give the partially reduced indole and azaindole products in 50% and 66% yield, respectively (in the case of entry 5, the



Scheme 3. Synthesis of **1** via three-component and four-component sequential Hantzsch reactions.

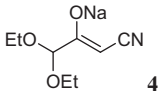
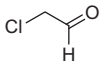
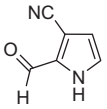
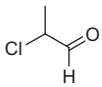
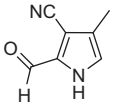
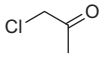
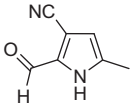
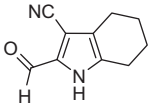
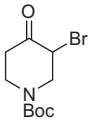
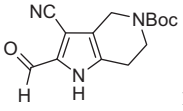
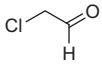
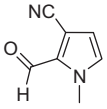
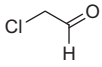
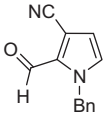
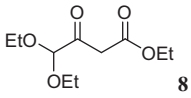
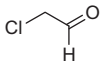
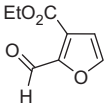
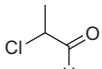
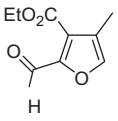
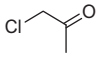
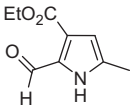
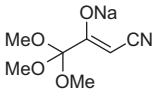
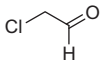
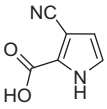
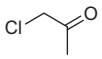
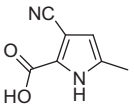


Scheme 4. Possible mechanism for the formation of pyrrole **1**.

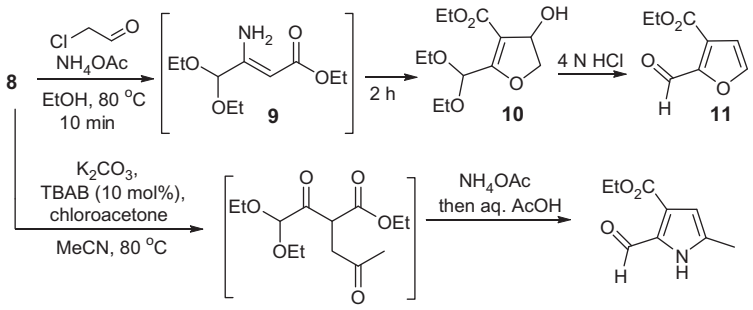
bromo-ketone was used simply on the basis of availability). These are particularly useful as potential building blocks as they introduce an element of three-dimensionality into the molecule, and in the case of entry 5, an additional point of reactivity to diversify the product of the reaction through the cyclic amine. Replacement of ammonium acetate with primary amines/acetic acid (entries 6 and 7) gave the N-substituted pyrroles in comparable yields to ammonia, circumventing the need for subsequent pyrrole N-alkylation.

We next attempted the reaction using the ethyl ester analogue of **4**. During preparation, it was found to be difficult to isolate this compound as its sodium salt; however the acidified form **8**

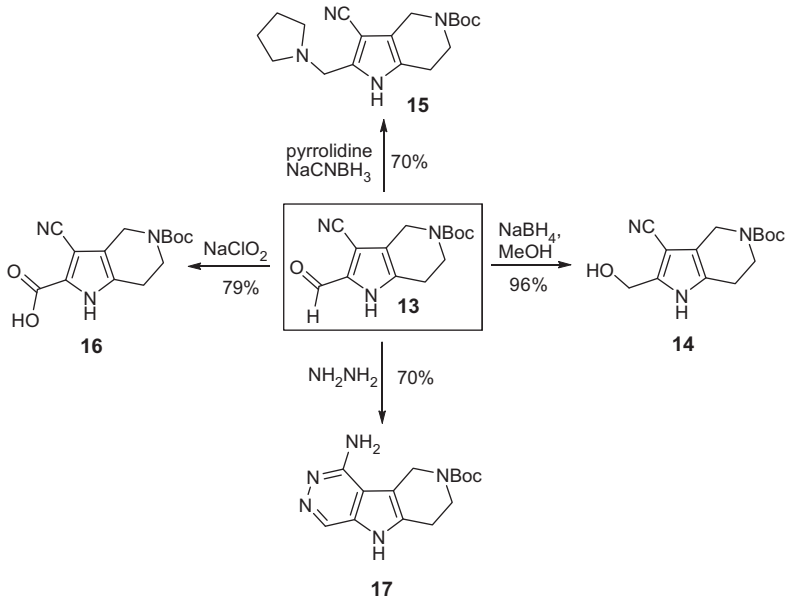
Table 1
Scope of the Hantzsch reaction[a]

Entry	Enolate	Chloro-carbonyl	Amine	Product	Yield[b] (%)
1	 **4**		NH_4OAc		51
2	**4**		NH_4OAc		45
3	**4**		NH_4OAc		55
4	**4**		NH_4OAc		50
5	**4**		NH_4OAc	 **13**	66
6	**4**		$MeNH_2$/AcOH		44
7	**4**		$BnNH_2$/AcOH		49
8	 **8**		NH_4OAc		46
9	**8**		NH_4OAc		44
10[c]	**8**		NH_4OAc		56
11	 **12**		NH_4OAc		0
12[d]	**12**		NH_4OAc		38

[a] Reaction conditions: enolate (1 equiv, 2.5 mmol), chloro-carbonyl (1.5 equiv), NH_4OAc (3 equiv), EtOH (12 mL), 80 °C, 1 h, then 80% AcOH in H_2O, rt.
[b] Isolated yield after column chromatography.
[c] Alternative reaction conditions were used: keto-ester (1 equiv, 2.5 mmol) was stirred with K_2CO_3 (1 5 equiv), TBAB (0.1 equiv) and chloroacetone (1.2 equiv) in MeCN (12 mL) at 70 °C for 2 h, then NH_4OAc (3 equiv) was added and heating was continued for 1 h. Acetal hydrolysis was then performed as normal with aq AcOH.
[d] The reaction was stirred for 4 h. Orthoformate hydrolysis occurred during the reaction, 80% aq AcOH was not added.



Scheme 5. Formation of furan **11** through a Feist–Bénary type reaction, and formation of the pyrrole through an alkylation/condensation sequence.



Scheme 6. Synthesis of fragment-like molecules from **13**.

appeared to be perfectly stable. When subjected to the Hantzsch conditions, some unexpected observations were made. Initially the enamine **9** was quickly formed, which was stable and could be readily isolated. On further heating with chloroacetylaldehyde, a more polar product was obtained which was identified as the 4-hydroxydihydrofuran **10**. This was found to be surprisingly stable to aromatization by elimination of water under mildly acidic conditions. However, hydrolysis with 4 N aq HCl solution led to rapid dehydration with concomitant unmasking of the aldehyde moiety to give ethyl 2-formylfuran-3-carboxylate (**11**) in respectable yield (46%). It was initially thought that the presence of base in **2** (as it is used as the sodium salt) may affect the nature of the products formed, however initial treatment of **8** with 1 equiv of sodium hydride followed by the normal reaction conditions still resulted in the furan product being isolated. Although the required compound **2** was not available through this method, the synthesis of the furan was notable as 2,3-dicarbonylated furans are as equally unexplored as their pyrrole analogues in the literature. In practice, ester substituted pyrrole **2** could be readily accessed from **1** by hydrolysis of the nitrile and then esterification of the acid. The formation of intermediate **10** and subsequent aromatization to the furan **11** are consistent with the mechanism of the Feist–Bénary furan synthesis.[15] This does not usually involve enamine formation, which would be expected to give the corresponding pyrrole (Scheme 5). 2-Chloropropanal also gave the furan product (entry 9), although when chloroacetone was used only the enamine intermediate **9** was obtained, which is presumably due to the greater reactivity of the aldehyde compared with the ketone. Ester analogue **8** and chloroacetone could however be transformed into the pyrrole by a sequential alkylation with potassium carbonate and catalytic TBAB in MeCN followed by treatment with ammonium acetate in a one-pot procedure (entry 10).

Finally, the reaction was conducted with a masked carboxylic acid moiety (compound **12**, entries 11 and 12). This proved to be a much less reactive nucleophilic component than **4**, nonetheless the carboxylic acid substituted pyrrole was obtained in a slightly reduced yield of 38% with chloroacetone (entry 12). In this case, the orthoformate hydrolysed completely during the reaction, so subsequent treatment with aqueous acetic acid was not necessary. No pyrrole products were obtained with chloroacetylaldehyde (entry 11), however the aldehyde products were readily oxidized to the carboxylic acid if this oxidation state was required (see Scheme 6).

Having established the generality of the route to fully functionalized pyrroles, we demonstrated their general utility as a platform to pyrrole based fragment-like molecules. Treatment of **13** with sodium borohydride selectively reduced the aldehyde in near-quantitative yield, whilst treatment with pyrrolidine and sodium cyanoborohydride smoothly gave the reductive amination product **15** in 70% yield. The aldehyde could be readily oxidized to the carboxylic acid **16** with sodium chlorite, whilst treatment with hydrazine resulted in a simultaneous condensation/intramolecular cyclization to give the tricycle **18** (Scheme 6). The Boc protecting

group in all of these products could be readily removed with HCl in 1,4-dioxane.

In conclusion, we have shown that a three-component, one-pot Hantzsch approach can give pyrroles and furans bearing differentially reactive carbonyl moieties at the 2- and 3-positions, a hitherto challenging substitution pattern to access.[16] Keto-nitrile compound **4** reacted with a range of halo-carbonyls to give bis-, tri- and polysubstituted pyrroles in reasonable yields. Interestingly, its ester analogue **8** formed the corresponding furan, probably through a Feist–Bénary type mechanism. As demonstrated, the products contain several handles for further manipulation and thus, this method should find use in total synthesis and medicinal chemistry campaigns.

References and notes

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16. *Representative procedure for the synthesis of **1**:* Enolate **4** (485 mg, 2.5 mmol) was stirred in EtOH (12 mL) with NH_4OAc (578 mg, 7.5 mmol). After 5 min the solids had fully dissolved. At this point, chloroacetylaldehyde (50% in H_2O, 0.48 mL, 3.75 mmol) was added and the reaction was warmed to 80 °C for 1 h. Following cooling to room temperature, AcOH–H_2O (4:1, 10 mL) was added and stirring was continued for 30 min. The volatiles were removed under vacuum and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The aqueous was extracted once with CH_2Cl_2, and the combined organics were dried over Na_2SO_4 and concentrated. The dark residue was purified by silica gel chromatography [heptane/EtOAc, 9:1–3:1] to give 2-formylpyrrole-3-carbonitrile (**1**) as an off-white solid, 153.5 mg, 51%. Mp 146–148 °C; ν_{max} (cm^{-1}) 2995 (w), 2235 (w), 1685 (s), 1410 (w), 1360 (s), 1185 (m); ^1H NMR (400 MHz, $CDCl_3$] 6.68 (t, 1H, J = 2.7, $CH_{Pyrrole}$), 7.15 (td, 1H, J = 1.0, 2.8, $CH_{Pyrrole}$), 9.81 (d, 1H, J = 1.0, $CH_{Aldehyde}$), 10.03 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) 98.73 (C_{Ar}), 114.72 (CN), 115.09 (CH_{Ar}), 126.58 (CH_{Ar}), 135.36 (C_{Ar}), 177.99 (CHO); m/z (EI) 120 [$(M+H)^+$, 100%)], 92 (45), 64 (25); HRMS (EI) $[M+H]^+$ 120.0392, $C_6H_4N_2O$ requires 120.0324.