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HANTZSCH PYRROLE SYNTHESIS ON SOLID SUPPORT

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Abstract: An efficient method for solid-phase synthesis of pyrroles is described. Polystyrene Rink amide resin is acetoacetylated and converted into polymer bound enaminones upon treatment with primary amines. These then undergo a Hantzsch reaction with α-bromoketones to yield pyrroles. After cleavage with 20% trifluoroacetic acid in dichloromethane pyrrole-3-carboxamides are obtained in excellent purity.

In recent years combinatorial chemistry and solid-phase organic chemistry (SPOC) have been established as important tools in the drug discovery process and are therefore of significant relevance to medicinal chemistry.[1] Due to the fact that heterocycles are common structural elements in a large number of biologically or pharmacologically relevant molecules extensive efforts in SPOC are being devoted for the development of solid-phase synthetic routes leading to heterocyclic systems.[2]

The Hantzsch pyrrole synthesis[3] is an alkylation-cyclocondensation reaction involving a primary amine, a β-ketoester or β-ketoamide and an α-bromoketone leading to tetra- or pentasubstituted pyrroles. The reaction can be performed either as a three component reaction or preferably in a two component pathway by first treating a primary amine with a β-ketoester or β-ketoamide to obtain an enaminone followed by reaction with an α-bromoketone to afford the pyrrole ring. In this work we present the solid-phase synthesis of pyrroles[4] following this classical synthetic route first described by Hantzsch.[5]

We proposed to synthesize the β-ketoamide component in the form of polymer bound acetoacetamide and to use the primary amine and the α-bromoketone for the introduction of diverse functionalities into the pyrrole ring. We chose Polystyrene Rink Amide AM resin[6] as solid support as it can be readily subjected to acetoacetylation to afford the desired polymer bound acetoacetamide. Acetoacetylation was carried out under three different experimental conditions as outlined in Scheme 1 (diketene acetone adduct[7] in NMP at 110 °C, diketene[8] in DCM and N-hydroxysuccinimidylacetoacetate/diisopropylethylamine). All of these methods resulted in the complete conversion of the amino groups (determined by ninhydrin test) into the corresponding amides **1**. However, for the preparation of the pyrrole collections we preferred to use diketene for the acetoacetylation step owing to its low cost and mild reaction conditions.

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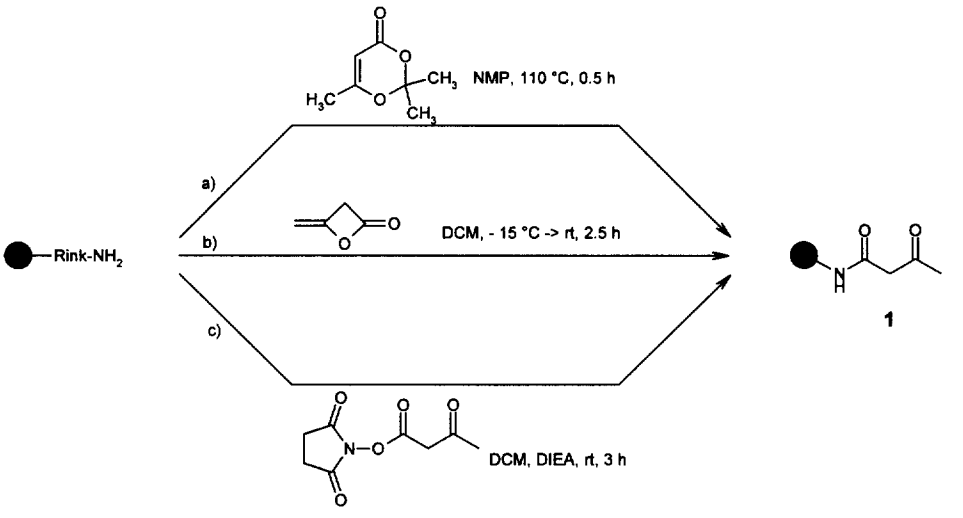
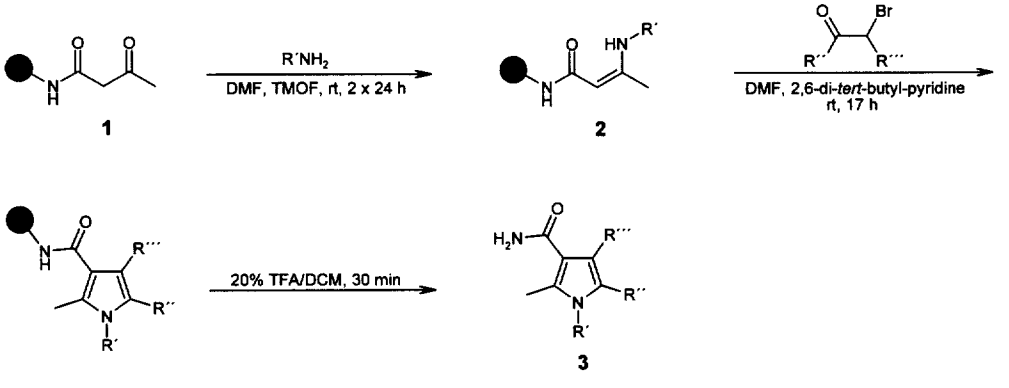


Scheme 1. Acetoacetylation of Rink amide resin

The first variable substituent was then introduced by reacting resin **1** with a variety of primary amines in the presence of trimethylorthoformate (TMOF) as dehydrating agent to get enaminones **2** as substrates for the introduction of further variation sites in the subsequent Hantzsch synthesis (Scheme 2). The reaction conditions for these steps were optimized by using 2-phenylethylamine and phenacylbromide. By carrying out reactions in different solvents (DMF, NMP, THF, toluene, dioxane) and by testing different bases (DIEA, pyridine, 2,6-di-*tert*-butyl-pyridine[9]), 2,6-di-*tert*-butyl-pyridine in DMF at room temperature turned out to be optimal conditions for obtaining pyrroles of high purity. Finally cleavage with 20% TFA in DCM resulted in the formation of the pyrrole-3-carboxamides **3**.[10]



Scheme 2. Hantzsch pyrrole synthesis on solid support

The scope and limitations of the reaction were then evaluated by varying the amine and the α-bromoketone input of the reaction. All compounds were analysed by HPLC, EI-MS and for some representative examples by NMR.[11] The analytical data of various pyrroles (Table 1) showed that the reaction worked well with a wide range of primary amines and α-bromoketones. Typical yields ranged from 4–11 mg of crude product starting from 50 mg of resin. Hydroxy functions (entries 15 and 16) and weakly nucleophilic tertiary amino groups in the side chain of the primary amine (entry 17) did not lead to any side reactions. Histamine as the amino component (entry 18) however did not give the desired product. In this case the main products were substituted pyrroles in which the imidazole ring is mono- or bisalkylated due to the excess of α-bromoketone. Aliphatic, electron rich or electron poor aromatic α-bromoketones as well as desylbromide (entry 4) as an example for a disubstituted α-bromoketone were successfully employed. With the highly reactive bromopyruvic acid ethyl ester the reaction time could be reduced to 3 h.

Table 1. Representative results of the Hantzsch pyrrole synthesis on solid support

Entry	Amine	α-Bromoketone	MS (M + 1)[a]	Purity[b]
1	2-phenylethylamine	phenacylbromide	305	98%
2	2-phenylethylamine	2-bromo-4′-phenylacetophenone	381	96%
3	2-phenylethylamine	2,5-dimethoxyphenacylbromide	365	91%
4	2-phenylethylamine	desylbromide	381	96%
5	2-(3,4-dimethoxyphenyl)-ethylamine	4-chlorophenacylbromide	399	95%
6	cyclopropylamine	3-nitrophenacylbromide	286	95%
7	cyclopropylamine	4-cyanophenacylbromide	266	97%
8	piperonylamine	1-bromo-2-butanone	287	94%
9	piperonylamine	5-(bromoacetyl)-3-(2,4-dichlorophe-nyl)isoxazole	470	85%
10	1-butylamine	bromopyruvic acid ethyl ester[c]	253	85%
11	2-furfurylamine	3,4-dichlorophenacylbromide	349	93%
12	thiophene-2-ethylamine	3-methoxyphenacylbromide	341	97%
13	allylamine	4-fluorophenacylbromide	259	97%
14	propargylamine	α-bromo-2-acetonaphthone	289	95%
15	tyramine	4-chlorophenacylbromide	355	94%
16	2-aminoethanol	4-diethylaminophenacylbromide	316	96%
17	N-(2-aminoethyl)morpholine	4-nitrophenacylbromide	359	92%
18	histamine	phenacylbromide	-	0%

[a]electrospray ionization; [b]purity was determined by C18 RP HPLC at 214 nm ; [c]reaction time: 3 h

In summary, we have described an efficient and facile solid phase synthesis of pyrroles starting from polymer bound acetoacetamide following the Hantzsch method. The synthesis takes place under mild conditions and is amenable to automation. Taking further into account the commercial availability of primary amines and α-bromoketones, this strategy can be ideally used for the synthesis of large combinatorial libraries. We are currently working on the use of the polymer bound enaminones for further heterocyclic syntheses and results will be reported in due course.

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References and Notes

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10. *Typical procedure:* Rink Amide AM PS (1% DVB) resin (50 mg, capacity: 0.57 mmol/g) is suspended in DCM (500 μL). A solution of diketene (15 μL) in DCM (250 μL) is added at 0 °C. After stirring for 30 min at 0 °C and 2 h at room temperature the resin is washed and suspended in DMF (600 μL). Trimethylorthoformate (62 μL) and 2-phenylethylamine (36 μL) are added. After 24 h at room temperature, the resin is washed with DMF and this step is repeated once. The resulting resin-bound enaminone is washed and suspended in DMF (1000 μL) and 2,6-di-*tert*-butyl-pyridine (26 μL) and phenacylbromide (23 mg) are added. The suspension is shaken for 17 h at room temperature and the resin is washed with DMF, THF, DCM, MeOH, Et_2O. Cleavage is performed with 20% TFA in DCM for 30 min. The solution is concentrated to dryness to provide the crude pyrrole which is then lyophilized from *tert*-butyl alcohol/water (4/1).
11. NMR data for entry 17: ^{1}H NMR (DMSO-d_6, 250 MHz) δ 2.63 (s), 3.73 (b), 4.34 (m), 6.85 (s), 7.69 (d), 8.32 (d). ^{13}C NMR (DMSO-d_6) δ 10.9, 31.3, 51.5, 63.7, 111.4, 116.4, 124.1, 128.9, 130.1, 136.7, 138.7, 146.0, 166.2.