Microwave Assisted Synthesis of 2,4,6-trisubstituted Pyrimidines from Acid Chlorides via *in situ* Formed Alkynones Utilizing Encapsulated Pd(II) as catalyst

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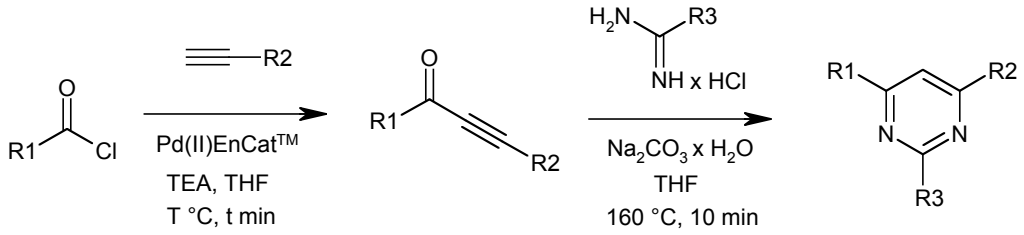
Introduction

Pyrimidines constitute a prominent class of heterocycles and their derivatives show interesting pharmacological properties. One synthesis approach, which has attracted attention, is the reaction of alkynones and amidinium salts[1].

Alkynones can be prepared by a Sonogashira type reaction from acid chlorides and terminal alkynes. Recently a copper-free method was reported[2]. The copper-free reaction conditions have the advantage that the formation of undesired 1,3-butadiyne derivatives is avoided. The authors further found that the cross-coupling reactions could be performed with palladium(II) acetate as catalyst under ligandless conditions giving good to excellent yields.

These findings encouraged us to try a synthesis route from acid chlorides via *in situ* formed alkynones to pyrimidines under microwave conditions. As catalyst for the cross-coupling reaction we chose palladium(II) acetate microencapsulated in a polyurea matrix,[3] **Pd(II)EnCat™**. This reagent showed certain benefits in handling, especially when applying microwave conditions: the risk of hot-spot overheating due to metal sticking to the vial glass wall was eliminated. The procedure of filtering off the catalyst became easier as well.



Scheme

Results and Discussion

The cross-coupling reaction between benzoyl chloride and 4-ethynyltoluene was used as a model for the optimization of the alkynone formation, and performed at 0.2 mmol scale. The reaction was heated by microwaves in Emrys™ Optimizer in the presence of TEA with Pd(II)EnCat™ as catalyst and THF as solvent. An LC-MS purity of the reaction mixture of >80 % was obtained within 15 min at 90 °C when reacting equimolar amounts of acid chloride and alkyne using 3 equiv. of TEA and 2

mol% catalyst. The encapsulated catalyst was subsequently filtered off easily using an ordinary filter frit.
In the following pyrimidine forming step the reaction with benzamidinium chloride was used as a model for the optimization.
When 1.2 equiv. amidine hydrochloride and 2.4 equiv. Na_2CO_3 x H_2O were added to the filtered alkynone solution and the resulting mixture was heated in microwaves at 160 °C for 10 min, an LC-MS purity of the reaction mixture of >90 % was obtained (Scheme).

Entry	Acid chloride R1	Alkyne R2	T °C	t min	Amidine R3	Pyrimidine Overall isolated yield, %
1	Phenyl	4-Me-phenyl	90	15	Phenyl	81
2	Phenyl	4-Me-phenyl	90	15	Methyl	81
3	Phenyl	4-Me-phenyl	90	15	PhO-Me	66
4	Phenyl	4-MeO-phenyl	90	15	Phenyl	74
5	Phenyl	4-MeO-phenyl	90	15	Methyl	76
6	Phenyl	Phenyl	90	15	Phenyl	74
7	Phenyl	Phenyl	90	15	Methyl	73
8*	Phenyl	Phenyl	90	15	Methyl	71
9	2-Me-phenyl	4-Me-phenyl	90	15	Phenyl	73
10	2-Me-phenyl	4-Me-phenyl	90	15	Methyl	77
11	2-F-phenyl	4-Me-phenyl	90	15	Phenyl	49
12	2-F-phenyl	4-Me-phenyl	90	15	Methyl	54
13	4-Azo-phenyl	4-Me-phenyl	100	30	Phenyl	52
14	4-Azo-phenyl	4-Me-phenyl	100	30	Methyl	50
15	4-NO_2-phenyl	4-Me-phenyl	90	15	Phenyl	49
16	4-NO_2-phenyl	4-Me-phenyl	90	15	Methyl	59
17	tert-Butyl	4-Me-phenyl	90	15	Phenyl	69
18	tert-Butyl	4-Me-phenyl	90	15	Methyl	83

* Scaled up 16 times
Table

In the subsequent syntheses some modifications of the optimized protocol showed to be necessary (entries 13-18, Table).
The alkynone formation in entries 13 and 14 required 1.5 equiv. of acid chlorides and prolonged reaction time (30 min) at a slightly higher temperature (100 °C).
In entries 15-18 the excess of acid chlorides was increased to 3 equiv., and 3 equiv. of the amidinium chlorides were required as well.

The formed pyrimidines were purified by chromatography on a Horizon™ HPFC™ System using a FLASH 12+M prepacked silica cartridge.

One of the syntheses was uniformly scaled up 16 times (3.2 mmol, entry 8) with microwave heating in Emrys™ Optimizer EXP. The result after purification by chromatography on a Horizon™ HPFC™ System using a FLASH 25+M prepacked silica cartridge was comparable with the 0.2 mmol synthesis (entry 7).
The resulting isolated overall yields are summarized in the Table

General experimental procedure

A 2 mL reaction vial loaded with a mixture of 0.2 mmol acid chloride, 0.2 mmol alkyne, 0.004 mmol Pd(II)EnCat™ (0.4 mmol Pd/g), of 0.6 mmol TEA and 1.0 mL THF was capped and heated to 90 °C in Emrys Optimizer™ for 15 minutes. After cooling, the vial was decapped and the catalyst was filtered off. To the resulting THF solution, loaded in a 2 mL reaction vial, 0.24 mmol amidinium hydrochloride and 0.48 mmol Na_2CO_3 x H_2O were added. The mixture was heated to 160 °C in Emrys™ Optimizer for 10 minutes. After cooling, the vial was decapped, the solid was filtered off and the solution was concentrated. The residue was purified by chromatography on a Horizon™ HPFC™ System using a FLASH 12+M prepacked silica cartridge. The products were analyzed by LC-MS and characterized by ^{1}H-NMR. The purities of the isolated pyrimidines were all found to be >95 %.

Conclusion

In this poster we describe a two step microwave-assisted synthesis method for the preparation of 2,4,6-trisubstituted pyrimidines. In the first step, the intermediate alkynone was synthesized by reacting an acid chloride with a terminal alkyne in a Sonogashira type cross-coupling reaction. The cross-coupling was, however, performed without addition of copper salts and with ligandless palladium as catalyst. Furthermore, we used a palladium catalyst microencapsulated in a polyurea matrix, **Pd(II)EnCat™**, which facilitated the handling. In the second step the formed alkynone was reacted without purification with amidinium chloride giving the desired pyrimidine. The total reaction times were 25-40 minutes and the overall isolated yields after chromatography were in the interval 49-83%.
One of the syntheses was uniformly scaled up 16 times and the resulting overall yield was comparable with the small scale reaction.

References:
1. Karpov, A. S. and Müller, T. J. J. Synthesis **2003**, 18, 2815
2. Alonso, D. A.; Nájera, C. and Pacheco, M. C. J. Org. Chem. **2004**, 69, 1615
3. The microencapsulated Pd catalyst, **Pd(II)EnCat™**, is available from Avecia Ltd

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