A Convenient Microwave Assisted Organic Synthesis of 1,3,5-Triarylobenzenes by Cyclotrimerization of *in-situ* formed Enaminones

Ronny Lundin and Panagiotis Ioannidis
Biotage Sweden AB, Kungsgatan 76, SE-753 18 Uppsala, Sweden

Introduction

Condensation reactions between *N,N*-dimethylformamide diethyl acetal, DMFDEA, and compounds comprising an activated methyl or methylene group adjacent to a keto functionality form alkylaminopropenones. These compounds have been used as versatile intermediates for the synthesis of a large number of heterocycles both with conventional and microwave heating[1,2].

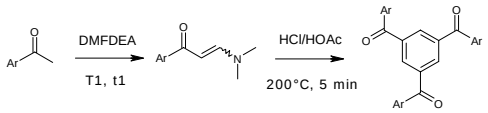
Recently Elghamry[3] described the synthesis of 1,3,5-triaroylbenzene derivatives in excellent yields by refluxing aromatic alkylaminopropenones in pyridine/acetic acid for 2 hours.

Since we earlier had synthesized alkylaminopropenones and alkylaminopropenoates under microwave conditions, we decided to try to design a one-pot synthesis procedure of 1,3,5-triaroylbenzene derivatives from the arylketones via the *in-situ* formed alkylaminopropenone intermediate.

Results and discussion

N,N-dimethylformamide diethyl acetal, DMFDEA (2.5 mmol), was reacted with an appropriate aryl ketone (2.5 mmol) without any addition of solvent in Smith Synthesizer™. (*Scheme 1*). The temp./time conditions were 180 to 220 °C for 10 to 12.5 minutes depending on the structure of the ketone. The reaction showed complete conversion according to LC-MS.
Conc. HCl (2.5 mmol) in 2 mL of acetic acid was added to the formed intermediate and the mixture was heated in Smithsynthesizer at 200 °C for 5 minutes. Optimization experiments showed that the use of HCl/acetic acid gave better results in the cyclotrimerization under microwave conditions than pyridine/acetic acid, which was stated by Elghamry for the conventionally heated reaction.

After reaction, the solvent was removed *in vacuo* and the residue was purified by chromatography on Horizon™ HPFC™ System using a FLASH 12+M prepacked silica column cartridge. All isolated products were characterized by ^{1}H-NMR. The results are summarized in *Table 1*.



Scheme 1

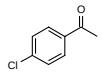
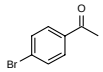
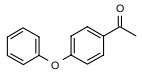
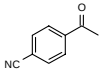
Ketone	T1 [°C]	t1 [m]	Yield after chrom. %	Purity, LC-MS %
	180	10	81	100
	180	10	91	98
	180	10	82	98
	220	12.5	71	98
	180	10	39	98
	200	12.5	75	99

Table 1

As a comparison we also tried the cyclotrimerization from purified aminopropenones The intermediates were thus purified by chromatography on Horizon™ HPFC™ System using a prepacked silica column cartridge, and characterized by ^{1}H-NMR. The purified intermediates were then subjected to the same cyclization procedure as stated above.

The products were washed with water, dried, weighed and analyzed without further purification. All isolated products were characterized by ^{1}H-NMR. The results are summarized in *Table 2*.

The outcome of the two experiment sets shows that the one-pot synthesis from aryl ketones to the triaroylbenzenes, without isolation of the intermediate, resulted in yields in the interval 71-91% after chromatographic purification, with the exception of the 4-cyano derivative which was obtained in 39% yield (*Table 1*).

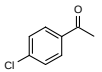
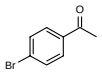
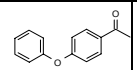
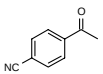
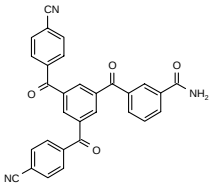
Ketone	Yield after aq. wash %	Overall yield after aq. wash %	Purity LC- MS %
	100	89	97
	100	85	95
	97	84	93
	100	81	99
	100	81	68
	97	82	98

Table 2

The synthesis from chromatographically purified intermediates gave overall-yields in the interval 81-89% with acceptable purity after washings with water. The 4-cyano derivative was however of poor purity, 68% (*Table 2*).

Further chromatographic purification resulted in a 98% pure (LC-MS) material in an overall-yield of 54%. The major by-product in the cyclotrimerization of the 4-cyano ketone was isolated, characterized (LC-MS, ^{1}H-, ^{13}C-NMR) and found to be:



Conclusion

We describe in this poster a microwave-assisted one-pot procedure for the two-step synthesis of triarylobenzenes from aryl ketones with a total reaction- time of 15-17.5 minutes and isolated yields generally in the interval 71-91%.
As a comparison, the synthesis was also performed in a regular two step manner with purification and isolation of the enaminone intermediate, which gave isolated overall yields generally in the interval 81-89%.
The last cyclotrimerization step was completed within 5 minutes and the isolated yields calculated from the purified intermediates were almost quantitative.

References:
1. Stanovnik, B. and Svete, J. *Synlett* **2000**, 1077
2. Westman, J.; Lundin, R.; Stålberg, J.; Östbye, M.; Franzén, A. and Hurynowicz, A. *Combin. Chem. High Throughput Screen* **2002**, *5*, 565
3. Elghamry, I. *Synthesis* **2003**, 2301

http://www.biotage.com

Biotage