Rapid Homogeneous Phase Sonogashira Coupling Reactions Using Controlled Microwave Heating

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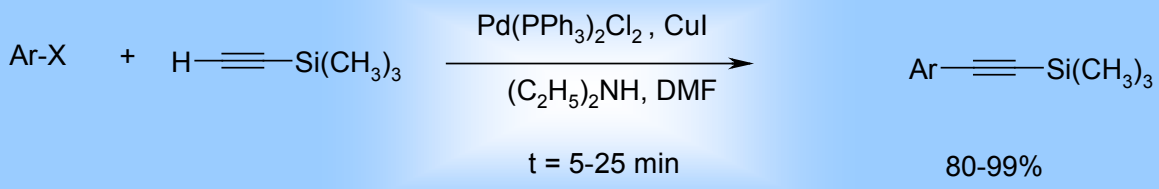

Introduction

Using combinatorial methods fast preparation of a large variety of chemical entities is possible. The automatisation of parallel synthesis, purification and analysis of the products is the source of the high speed of this method. However, the effectiveness is still limited by the rate of chemical reactions. Thus, attempts to make further improvements would have to address this weakness in drug discovery.

Arylalkynes

Arylalkynes, the products of the Sonogashira coupling reaction, are interesting intermediates for the preparation of a variety of target compounds. Recent examples include heterocyclic compounds, molecular scale electronic devices, cyclophanes, estradiol derivatives, enediyne antibiotics, and natural products with antitumor or phytotoxical activity. Some weaknesses of the coupling conditions published earlier in the literature are the demand for a reactive arene derivative and long reaction times.

Sonogashira coupling

We have developed fast, reliable homogeneous reaction conditions for the Sonogashira coupling. They use microwave irradiation under controlled conditions, with monitoring of temperature, pressure and irradiation power. We have achieved coupling of aryl iodides, bromides, triflates, an aryl chloride, as well as pyridine and thiophene derivatives with trimethylsilyl acetylene. Excellent yields for substrates containing a large variety of substituents in different positions were obtained in 5-25 minutes. The same yields could also be obtained when using conventional heating.

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Representative examples

	This work	Literature	
Ar-X	Yield	Yield	Conditions
2-iodoaniline[a]	92%	96%	20h, 25°C
3-iodoaniline[a]	99%	72%	20h, 25°C
4-iodoaniline[a]	98%	90%	18h, 25°C
4-bromoaniline[b]	87%	-	-
2-bromoanisole[b]	87%	61%	48h, reflux
4-cyanophenyl-triflate[a]	99%	97%	3h, 25°C
3-iodothiophene[a]	88%	80%	-
3-bromothiophene[b]	81%	28%	4h, heat
2-chloropyridine[b]	97%	80%	12h, 120°C

Conditions: [a] 5 min, 120 °C, [b] 25 min, 120 °C

Conclusion

The homogeneous reaction conditions developed for coupling of aryl halides and pseudohalides provide good to excellent yields within a few minutes, as compared to hours or days when literature procedures are applied. Using a *Smith Synthesizer*, the microwave assisted procedure can easily be automated.

Acknowledgement

We would like to thank the Swedish Technical Science Research Council for financial support and Personal Chemistry AB for access to SmithSynthesizer™.

Reference

Several examples and reaction conditions in detail are described in:
Erdélyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165.