

Automated Serendipity with Self-Optimizing Continuous-Flow Reactors

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A self-optimizing approach is used as a tool for targeting known and unknown materials in the continuous reaction of aniline, dimethyl carbonate (DMC) and tetrahydrofuran (THF) in supercritical CO_2 on γ -Al₂O₃. The study led to the formation of methylated anilines or carbamate derivatives and unusual addition products with THF including pyrrolidines and *N*-alkylated anilines. The identification of these

Introduction

Currently, there is increasing interest in minimizing the amount of waste generated in chemical processes.^[1] One source of such waste is the formation of byproducts.^[2] However, the time needed to characterize those byproducts often discourages all but the most persistent chemists from doing so. The aim of this Communication is to demonstrate that recent advances in flow chemistry, particularly the development of self-optimizing reactors, not only can accelerate the identification of byproducts but also can lead to the discovery of unexpected reactions.^[3]

Self-optimizing reactors combine a computer-controlled continuous reactor with in-line analysis to adjust reaction conditions automatically to control the outcome of the reaction,^[4] see Figure 1. We have previously demonstrated that, for a reaction that can give rise to two different products, such a reactor can be optimized to maximize the yield of either product.^[4,5]

Here, we apply a self-optimizing approach to a more complex system, the three-component reaction of aniline, dimethyl carbonate (DMC) and tetrahydrofuran (THF), catalysed by γ -alumina and show that a relatively complete understanding of the various reactions can be obtained in quite a short time by systematically optimizing the yields of the different products and byproducts. In particular, we describe what appears to be a previously unreported reac-

University of Nottingham Ningbo China 199 Talking East Road, Ningbo 315100, China products leads to the development of a plausible mechanism for the reactions. The system not only demonstrates a high flexibility that the self-optimization approach provides, including the ability to optimize for a variety of products by using a single catalyst, but also the ability to discover unexpected and original synthetic reactions.

tion between these three compounds, possibly one of the first reported examples of a new reaction being discovered by flow chemistry.^[3,6]

We have discussed in some details the different optimization strategies,^[4,5] and here we focus on their chemical consequences. In general, we used the same range of conditions for all experiments and a Super Modified Simplex (SMSIM) algorithm to modify the reaction parameters.^[7] As SMSIM is a local algorithm, the final result might depend on the starting conditions. We deliberately used errors in sampling to make sure the optimization did not get stuck in local minima.

Results and Discussion

The initial rationale for studying the reaction of aniline with DMC was a modest extension of our previous work on the catalytic etherification of alcohols in supercritical CO₂.^[4a,5,10] However, an immediate problem arose; there were frequent blockages in the pipework. Therefore, THF was added as a co-solvent; such approach is well known to increase the solubility of compounds in non-polar supercritical fluids.^[11] The consequence was that the GC analysis of the unoptimized reaction by using the CO₂/THF solvent showed quite a complex mixture of products (see Figure 2a). Apparently, THF was acting as a reactant. Therefore, for subsequent optimizations, THF was replaced with toluene, which was expected to be inert under these reaction conditions, and a high yield of the expected product, N,Ndimethylaniline (1), could be obtained (see Figure 2c, Table 1, and Scheme 1).

Before starting the first series of optimizations, a temperature-ramp experiment was performed in order to find the lower limit at which the catalyst was starting to show some activity. The higher temperature limits were defined

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Figure 1. Schematic representation of a self-optimizing continuous-flow reactor equipped with four HPLC pumps and a reactor (preheater filled with sand and tubular reactor filled with catalyst). The output of the reactor is analysed by an in-line GC. The data from the analysis are fed into a computer, which applies the Super Modified Simplex (SMSIM) algorithm^[7] to calculate a new set of reaction parameters (e.g. temperature, pressure, flow rates, etc.), which is expected to give a higher yield of the desired product.^[8] The procedure is repeated iteratively until a maximum yield is obtained.^[9]



Figure 2. Optimization of the reaction of aniline with DMC in toluene. (a) GC trace of the initial product mixture (from aniline + DMC + THF); (b) trajectory of the optimization for 1 through parameter space (from aniline + DMC); (c) GC trace of the optimized product mixture for 1 and for 2, respectively (with aniline + DMC); for conditions see Table 1.

Table 1. Conditions optimized for the highest yields of 1–5 and 7–9 for reactions between aniline and DMC and/or THF.

Product	Selectivity [%]	Conversion [%]	Temperature [°C]	Aniline ^[a] flow [mLmin ⁻¹]	DMC flow [mLmin ⁻¹]	THF flow [mLmin ⁻¹]	DMC/aniline molar ratio	THF/aniline molar ratio
1 ^[b]	> 95	100	345 ± 5	0.17 ± 0.03	$0.5\pm0.1^{[a]}$	—	> 2.5	_
2 ^[b]	83 ± 8	85 ± 10	345 ± 5	0.25 ± 0.05	$0.35 \pm 0.05^{[a]}$	_	1.5-2.2	_
3 ^[c]	70 ± 10	50 ± 10	183 ± 3	0.2 ± 0.1	0.9 ± 0.1	_	> 150	_
4 ^[b,e]	45 ± 5	100	318 ± 5	0.16 ± 0.05	$0.50 \pm 0.05^{[a]}$	_	2.2-5	_
5 ^[d]	> 99	100	275 ± 15	0.15 ± 0.1	_	$0.3 \pm 0.1^{[a]}$	_	2.1-3.6
7 ^[c]	30 ± 5	85 ± 5	200 ± 10	0.2 ± 0.1	0.43 ± 0.08	0.65 ± 0.05	> 50	> 150
8 ^[c]	20 ± 5	100	235 ± 5	0.17 ± 0.08	0.5 ± 0.1	0.45 ± 0.15	> 90	> 100
9 [c]	6	72	196	0.16	1.05	0.46	280	130

[a] 0.275 m solution in toluene. [b] 10 MPa, $1 \text{ mLmin}^{-1} \text{ CO}_2$. [c] 20 MPa, $1 \text{ mLmin}^{-1} \text{ CO}_2$. [d] 10-12 MPa, $1.1 \pm 0.1 \text{ mLmin}^{-1} \text{ CO}_2$. [e] As a control, the reaction was repeated by using a niobium catalyst, Nb₂O₅·5H₂O, in place of γ -Al₂O₃; **4** was observed as an additional product (see Scheme 1); **4** was also produced in a separate experiment on Nb₂O₅ with a mixture of **1** + MeOH rather than DMC.^[15]

either by the equipment limitations or by safety restrictions. This was followed by a catalyst stability test under prolonged reaction time and at fixed conditions. The optimization was then typically started at conditions where the target product could be detected and contained within the fixed boundaries (see Exp. Sect.). $^{\rm [5a]}$

The highest yields of 1 were obtained with an excess of DMC at $345 \,^{\circ}$ C (Table 1). At that temperature, DMC is





Scheme 1. Catalytic reaction of aniline with DMC in toluene and $scCO_2$ to give 1–4.

likely to be decomposed into dimethyl ether (DME),^[12] which may well be the actual methylating agent. Conveniently, the flow rates of aniline and DMC and hence the reagent stoichiometry could be manipulated to give a high yield of *N*-methylaniline (2) at the *same* temperature (see Table 1).^[13] Compound 2 is relatively difficult to prepare by more conventional routes, which usually involve toxic reagents and generate significant amounts of waste.^[14] Similarly, a further optimization for a third reaction product, namely carbamate 3, led to a 70% selectivity (Table 1). The formation of 3 occurs at significantly lower temperature, where DMC is not fully decomposed and the addition of aniline to DMC is more likely to happen.

In most of the optimizations reported above, we have used toluene as a co-solvent as this appeared to give the cleanest route to the desired products, i.e. minimizing the byproducts. With this in mind, we decided to reinvestigate the effect of THF as a reagent on γ -Al₂O₃. To avoid potential blockages of the reactor, both aniline and THF were used as solutions in toluene. Flowing aniline and THF through the reactor *without* DMC led to the formation of N-phenylpyrrolidine (5) (Scheme 2). Optimization gave a > 98% yield of 5 at ratios of aniline/THF between 1:2.1 and 1:3.6 (see Table 1). Formation of 5 by reaction of aniline and THF was first reported^[16] in 1937, and it was then studied in more detail in 1990 by Hargis et al.^[17] who carried the reaction out continuously in the gas phase on a TiO₂ catalyst at low pressure. To the best of our knowledge, this is the first report of a continuous reaction of aniline and THF at high pressure and in scCO₂ providing a 10-fold increase in productivity compared to the earlier studies. Very recently during the preparation of this manuscript, Korbad and Lee^[18] have reported the formation of 5 with long reaction times in toluene and with stoichiometric amounts of the Lewis acid AlMe₃. Therefore, the reaction reported here has definite advantages in terms both of reduced waste and of higher productivity compared to previous routes to 5.



Scheme 2. Reaction of aniline with THF in toluene and $scCO_2$ to give 5.

A plausible mechanism for the formation of **5** proceeds via the intermediate^[19] **6**, which, even if it is formed, turned

out to be too reactive for isolation from our reaction mixtures (Scheme 3). Thus, attempts were made to trap 6 in the presence of DMC. GC analysis of the product mixture from the multicomponent system of aniline, THF and DMC indicated the presence of several additional products in small amounts. We therefore carried out optimization experiments for each of these, which led to the isolation and characterization of 7 (30% selectivity), 8 (20% selectivity) and 9 (6% selectivity). None of these compounds have been previously reported. They were separated from the reactor mixtures by chromatography and characterized by NMR spectroscopy (see Supporting Information). Their formation can be rationalized by an unusual sequence of nucleophilic substitutions (Scheme 3). Intermediate 6, obtained from a first THF alkylation, is susceptible to both N- and O-methylation to produce 7 or 8. The isolation of 7 suggests that O-alkylation is kinetically favored. In addition, 7 can react with an additional molecule of THF to produce 9. All of these reactions are likely to be essentially concurrent and happen under similar conditions. The main limitation in achieving higher selectivity is the fact that ring closure is always predominant and 5 is obtained as a major product. Alkylation is also in competition with the methylation/ carbamoylation processes, and 1, 2 and 3 are observed as well. Therefore, the optimization focuses on tuning the temperature; even so, optimum conditions for the formation of products 7-9 are similar (see Scheme 3).



Scheme 3. Plausible pathway for the reactions of aniline (in toluene), DMC and THF in $scCO_2$ yielding 5 and 7–9.

In addition it was found, somewhat surprisingly, that when **2** was used as the starting material for the reaction with THF, the major product observed was still **5** (75%) together with **1** (up to 25%; Scheme 4). *N*-Demethylation therefore seems to take place as an additional competitive pathway under these conditions.^[20]

Scheme 4. Proposed demethylation mechanism occurring during the reaction of **2** with THF, yielding **5** and **1**.

The reactions were repeated with Me-THF as the starting material and γ -Al₂O₃ as a catalyst yielding quantitatively 2-methyl-1-phenylpyrrolidine (**10**) (Scheme 5). How-

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ever, the range of optimized conditions were not as broad as in the case of THF; instead the system located an optimal point at 237 °C, 14.4 MPa, 1.16 mL min⁻¹ CO₂ and a 2-MeTHF/aniline ratio of 4.2. Addition of DMC to the reaction mixture with 2-MeTHF, enabled us to isolate and characterize product 11. It is therefore likely that the attack occurs on the less substituted carbon atom, most probably by an S_N2-type mechanism. We also showed that 11 can be an intermediate for the formation of 10, by pumping 11 into the reactor without other reagents and finding 10 as the sole product.



Scheme 5. Reaction of aniline with DMC and 2-MeTHF in toluene and $scCO_2$ to give 10 and 11.

Conclusions

Here we have shown that self-optimizing reactors enable chemists to switch the selectivity to different products in a chemically complex system by using γ -Al₂O₃ as a catalyst. The technology is capable of optimizing the yield of as yet uncharacterized products, ultimately leading to a better understanding of the chemistry. Hence it can be used for the development of new chemical transformations, as demonstrated here with the discovery of an original multi-component reaction sequence.

Studying the reactivity and selectivity of organic reactions can be complex and time-consuming, but it is a crucial step in helping organic chemists to devise better processes. It has been suggested^[21] that developing new chemistry in continuous systems is one of the major challenges in flow chemistry. Here we have demonstrated that self-optimizing reactors can provide an interesting and accelerated solution to this problem.

Experimental Section

CAUTION! The reactions described here involve high pressures and require equipment with the appropriate pressure rating.

General: All experiments were carried out by using a self-optimizing reactor (Figure 1), which has been described in detail previously.^[4a,5a] The conditions to produce the first simplex [(n + 1) vertices, *n* variables] were determined by the operator. After that, the measurement points were calculated by the SMSIM algorithm within the allowed ranges. The result of the reaction was determined by in-line GLC analysis (programme time 17 min) and the pressure was controlled by a back-pressure regulator at the outlet of the system.

Optimization for 1, 2 and 4: Ranges allowed: Organics 0.05– 2.0 mLmin^{-1} (0.275 M solutions in toluene); temperature 150–350 °C; CO₂ flow was set at 1 mLmin⁻¹ and pressure at 10 MPa.

Optimization for 3 and 7–9: Ranges allowed: Organics $0.1-2.0 \text{ mLmin}^{-1}$ (aniline 0.275 M in toluene, THF and DMC pure); temperature 150–300 °C; CO₂ flow was set at 1 mLmin⁻¹ and pressure at 20 MPa.

Optimization for 5, 10 and 11: Ranges allowed: Organics 0.01– 2.0 mLmin^{-1} (0.275 M solutions in toluene); temperature 150– $300 \text{ }^{\circ}\text{C}$; CO₂ flow 0.5–2 mLmin⁻¹; pressure 10–20 MPa.

Supporting Information (see footnote on the first page of this article): Further details including operating procedures, analysis and characterizations of all new compounds.

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