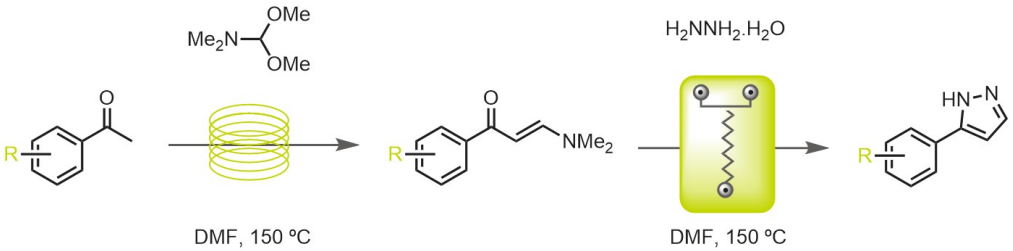
Technical Note

Two-Stage Synthesis of Pyrazoles from Acetophenones by Flow Chemistry

Abstract

As the pharmaceutical, fine chemical and cosmetic industries move from batch to continuous processes, so does the whole field of organic chemistry. Microfluidic technologies offer the bench chemist the opportunity to gain control over key reaction parameters and tackle complex transformations through new methodologies.

This Technical Note describes the efficient synthesis in flow of a library of pyrazoles through a two-step process, whereby a starting acetophenone is first condensed with DMADMF to form an intermediate enaminone, followed by a second condensation with hydrazine to generate the desired pyrazoles.



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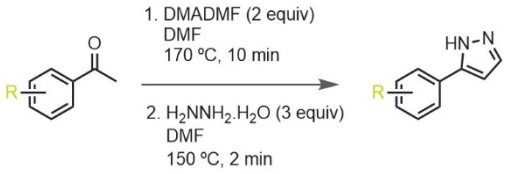
Flow Chemistry is a key enabling technology that has proven to be particularly advantageous for certain syntheses. Its inherent characteristics offer a wide range of benefits: reactions cannot only be performed faster, safer, and cleaner, with improved reproducibility and scalability, but continuous set-ups facilitate the integration of synthesis, purification, and analysis units, speeding up optimization, and even allowing for reaction conditions not possible in batch chemistry.[1] Drug discovery is an ever-evolving field, where new technologies such as flow or photo chemistry are allowing access to new regions of the chemical space. As always, innovation in organic synthesis lies in the wise combination of classical and state-of-the-art methodologies.

In this Note, we present a process developed in house for the efficient synthesis of substituted pyrazoles. Pyrazoles are an important and well represented chemotype in drug discovery,[2] displaying a wide range of biological activities, including analgesic, anti-inflammatory, antipyretic, tranquilizing, muscle relaxing, anticonvulsant, antidiabetic and antibacterial properties.

The project started with the exploration of different reactions. First, we developed a procedure for the synthesis of enaminones from acetophenones and DMADMF. After optimization of the reaction conditions, the method was successfully applied to the synthesis of a variety of enaminones in very good yields. This prompted us to further explore the possibility of using such enaminones as intermediates for more complex products, e.g. pyrazoles.

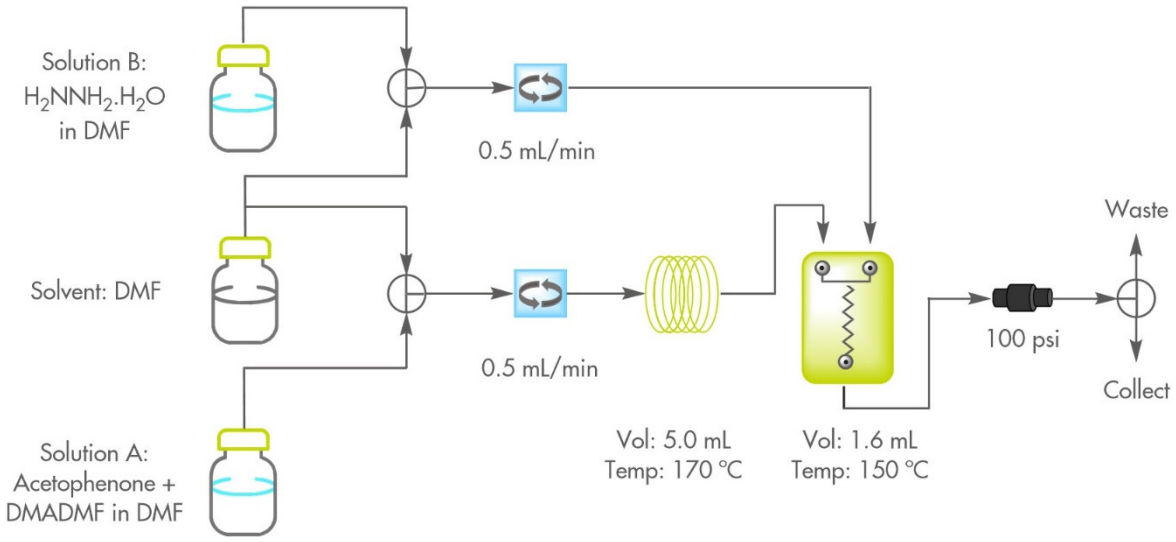
After optimizing the conditions for the second reaction, we designed the tandem reaction (Scheme 1). We opted for connecting in line a stainless-steel coil (5 mL) and a glass mixer-chip (2 mL), with a maximum operating range of 150 °C.



Scheme 1 Two-stage synthesis of pyrazoles from acetophenones in flow.

The idea was passing the acetophenone and DMADMF solutions in DMF through the steel coil at 170 °C with a flow rate of 0.5 mL/min, adding then the hydrazine solution in DMF into the chip at 150 °C (Scheme 2). The hydrazine solution would be added with a flow rate of 0.5 mL/min, so the total flow rate into the chip would be 1 mL/min and therefore the residence time for the second transformation is 2 min. For the synthesis of the enaminone, we would maintain the optimized conditions of 170 °C and 10 min.

System Set-up		
	Reactor 1	**Reactor 2**
Type	Coil	Chip
Material	Stainless Steel	Glass
Volume	5.0 mL	2.0 mL
Max Temp	260 °C	150 °C
Dead Vol.	0.60 mL	
Min Pressure	0.5 bar	
Max Pressure	30 bar	
Wash Flow Rate	5.0 mL/min	
Pump Start Delay	5 s	
Equil. Flow Rate	0.5 mL/min	
Loop. Vol.	2 mL	



Scheme 2 Schematic of the flow system set-up.

We started from a wide range of acetophenones with different stereoelectronic profiles to study the viability and scope of the process. All the experiments were performed with acetophenone concentrations ranging from 0.543 M to 0.624 M. In all the experiments, we used 2 equiv. of DMADMF for the first step and 3 equiv. of hydrazine for the second step. Therefore, the concentration of hydrazine in the second step is three times the concentration of acetophenone in the first step.

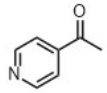
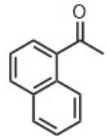
The concentrations, ratios, yields, run times, and throughputs for the synthesis of a series of pyrazole analogues prepared by this procedure are summarized in the Table below.

The results clearly show that, in the case of acceptor substituents in the acetophenone such as halogens (entries 10–14), the pyrazole yields are high, with no obvious effect of the substitution position.

In the case of donor (entries 2–4) and strong donors (entries 5–9) substituents, we found the substitution position to be more important, with lower yields obtained in the case of *para*-substituted acetophenones. The biggest effect was observed for strong donor groups like methoxy (entries 5–7). The effect of the 4-NBn_2 group (entry 9) is striking, but at the time we did not have other positional isomers of this product available to perform appropriate comparison.

In the case of 4-hydroxyacetophenone (entry 8), the product isolated was not the free phenol, but the *O*-methylated product (60% yield). This observation agrees with some publications on the methylation of phenols with DMADMF.[3] HPLC-MS analysis of the collected crude showed only traces of the free phenol. It seems that, under the reaction conditions for enaminone synthesis, the methylation process is much favored.

The transformation of the acetophenone bearing a 4-NHBoc group (entry 16) proceeded with high conversion, with several products observed by thin layer chromatography (TLC). Subsequent analysis by HPLC-MS of the collected crude showed the presence of the expected pyrazole (about 54%), with other three subproducts in 22%, 15% and 3.5% conversions. Purification of the mixture yielded two fractions, the main containing the expected pyrazole and a subproduct. The 1H-NMR spectrum of such byproduct revealed a similar structure to that of the expected product, but with an additional methyl group. The ratio of pyrazole/methylated-pyrazole was determined as 5:2 by NMR analysis. The minor fraction was identified as a deprotected derivative of the acetophenone, although its structure was not fully elucidated.

Entry	R	[Acetophenone]	Yield		Run time	Production rate	
		M	%	g	min	g/h	mmol/h
1	H	0.616	79	1.44			
2	2-Me	0.595	84	1.18	32	2.21	13.97
3	3-Me	0.595	83	1.17	32	2.19	13.84
4	4-Me	0.624	70	2.11	63	2.01	12.70
5	2-OMe	0.609	75	2.60	67	2.33	13.37
6	3-OMe	0.624	87	3.07	66	2.79	16.02
7	4-OMe	0.609	66	2.23	64	2.09	12.00
8	4-OH	0.623	60[1]	0.49	14	2.10	12.06
9	4-NBn_2	0.543	32	0.89	30	1.78	5.24
10	2-Br	0.595	92	1.72	29	3.56	15.96
11	3-Br	0.594	82	3.69	69	3.21	14.38
12	4-Br	0.609	86	3.89	72	3.24	14.53
13	2-Cl	0.609	90	2.85	57	3.00	16.80
14	4-F	0.624	81	0.41	12	2.05	12.64
15	4-CO_2Me	0.568	-[2]	-	-	-	-
16	4-NHBoc	0.568	-[3]	-	30	-	-
17		0.640	92	1.71	52	1.97	13.59
18		0.609	88	3.37	66	3.06	15.77

Acetophenone/DMADMF/Hydrazine hydrate ratio = 1:2:3. [1]The product obtained was the methylated phenol, 4-OMe. [2]The enaminone formed in the 1st step precipitated in the coil reactor and could not be processed further. [3]A complex mixture containing ca. 50% of the desired pyrazole and several other byproducts was obtained.

Finally, conversion of the acetophenone bearing a 4-CO_2Me group could not be achieved. Reaction of the ketone with DMADMF yielded a solid that clogged the system, preventing the completion of the second reaction. Nevertheless, the obtained reaction mixture was stored at r.t. for 14 h, after which we observed the precipitation of a solid that was identified as the expected enaminone by HPLC-MS.

Finally, to obtain further information on the scope of the method, we carried out two additional experiments with ketones derived from 1-naphthyl and 4-pyridyl fragments (entries 17 and 18). We were happy to observe still high yields, with no detection of the starting ketone by HPLC-MS.

In summary, we can conclude that the tandem synthesis of pyrazoles using flow chemistry is a general, high-yielding method, amenable to a wide range of substrates.

Even in the case of substrates that afforded low yields, we cannot discard the need to look for alternative reaction conditions. In those cases, optimization of the procedure would be focused on the enaminone formation, since this seems to be the step that influences the pyrazole yields. This hypothesis is based on the absence of the enaminone intermediate in the collected solutions, where in the few cases when these were detected, it was at very low concentrations, thus indicating that this intermediate reacts easily with hydrazine. Only in one instance, when the substrate was methyl(1-naphtyl) ketone, the corresponding enaminone was detected in significant amounts.

Nevertheless, the starting ketone was in some instances detected by TLC in the final mixtures. The most remarkable cases concern the substrates with strong donors in the *para*-position (4-NBn_2, 4-Me and 4-OMe). In these cases, the low pyrazole yields can be attributed to low conversions of the ketone into the enaminone, since no other relevant subproducts were detected.

References

1. Baumann et al., Org. Process Res. Dev. 2020, 24, 10, 1802–1813; Kirschning et al., Adv. Synth. Catal. 2012, 354, 17-57.
2. Shamsuzzaman et al. Review: Biologically active pyrazole derivatives. New J. Chem., 2017,41, 16-41.
3. Priefer et al. Tetrahedron Lett. 52 (2011) 2776–2779.

Some of the data here described have also been reported in Uniqsis Application Note 29. Cover image courtesy of Uniqsis Ltd.

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