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[3+2] Dipolar cycloadditions of an unstabilised azomethine ylide under continuous flow conditions

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ABSTRACT

The [3+2] dipolar cycloaddition reactions of the unstabilised azomethine ylide precursor benzyl(methoxymethyl)(trimethylsilylmethyl)amine with 12 electron-deficient alkenes in the presence of catalytic trifluoroacetic acid are examined under continuous flow conditions (20–100 °C, 10–60 min residence time). The more reactive and hazardous alkenes such as ethyl acrylate, *N*-methylmaleimide and (*E*)-2-nitrostyrene afford substituted *N*-benzylpyrrolidine products in 77–83% yields, whereas less reactive dipolarophiles such as (*E*)-crotononitrile and ethyl methacrylate give lower yields (59–63%). Under optimised conditions, the reaction with ethyl acrylate is scaled up to afford ethyl *N*-benzylpyrrolidine-3-carboxylate (30 g, 87%) in 1 h.

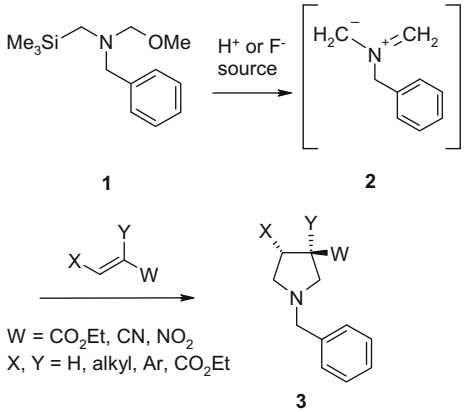
The [3+2] cycloaddition of an unstabilised azomethine ylide with an electron-deficient alkene[1] offers a succinct entry into substituted pyrrolidines (Scheme 1), which are considered valuable templates for the design of pharmaceuticals. A popular way to generate the required azomethine ylide **2** is from the silylated aminal ether **1**[2] in the presence of an alkene which traps the ylide to form the product pyrrolidine **3**. The reaction is concerted, consequently, the relative stereochemistry in the dipolarophile (*E* or *Z*) is carried forward into adduct **3** (trans or cis).

As an illustration of the ways in which the pyrrolidine structural motif has been employed in pharmaceuticals, a few recent examples are shown in Figure 1, including PDE9,[3] factor Xa,[4] rho kinase[5] and AKT protein kinase[6] inhibitors, H_4[7] and NK_3[8] antagonists, antiviral compounds[9] and MC4 agonists.[10]

Usually ylide generation is promoted by an acid or fluoride source.[11,12] One of the earliest and simplest of these consists of adding 10 mol % trifluoroacetic acid (TFA) to a mixture of the other reactants in toluene or dichloromethane solvent, with cooling if appropriate. Whilst these conditions have been safely scaled at Pfizer to >400 g for cinnamic ester derivatives (i.e., X = aryl, W = CO_2Me), the reaction becomes dangerously exothermic with more reactive dipolarophiles such as methyl crotonate and *N*-methylmaleimide.[13] One way around this problem is to pre-mix the dipolarophile and the TFA, and add the azomethine ylide precursor slowly to control the reaction temperature. Alternatively, the reaction can be moderated by a suspension of LiF in acetonitrile.

Reactions conducted under conditions of continuous flow can offer advantages over conventional batch reactions.[14] For example, mixing of reactants is reproducible and precise control of stoichiometry can be achieved. The relatively small reaction volume means greater safety through lower amounts reacting at any one time, particularly for highly hazardous reagents or exothermic reactions. The high surface area to volume ratio of narrow-gauge tubing helps rapid heat transfer and therefore control of reaction temperature.[15,16]

Rapid heat transfer aids exothermic reactions requiring high reactant concentrations for optimum yields. The major limitation in many continuous flow set-ups is the need for a homogeneous medium throughout the system; precipitates or insoluble reactants affect flow rates or cause blockages. Insoluble reagents or catalysts



Scheme 1.

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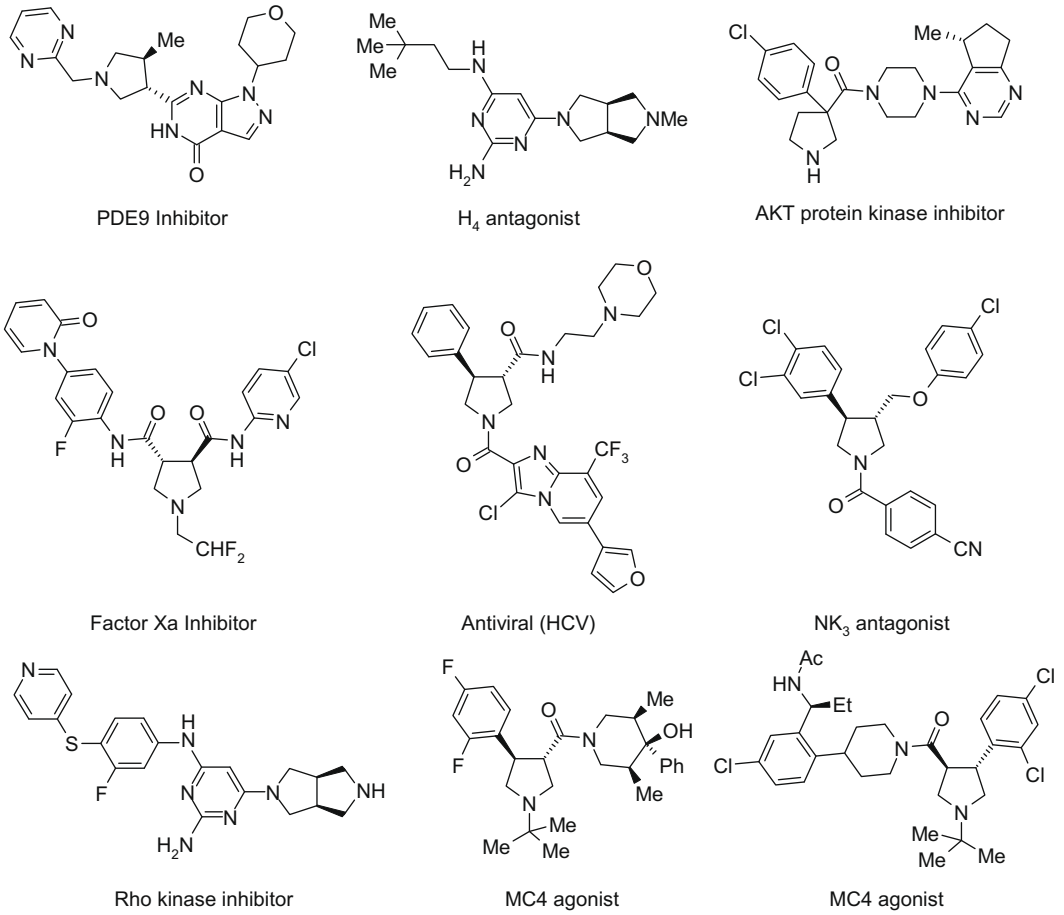


Figure 1.

can be introduced via in-line reagent cartridges, and excess reactants may be removed in a similar way, thereby facilitating product purification.[17] Finally, once the optimum reaction conditions have been developed, increased scale is achieved by running the reaction for longer or employing multiple reaction modules in parallel, whereas re-optimisation of batch reactions is frequently required as the scale is increased. Equipment is now commercially available for performing reactions on micro-,[18] meso-[19] and macro-scales.

We describe herein our investigations of the [3+2] cycloadditions of **2** with various dipolarophiles under conditions of continuous flow, since this would permit a high degree of control over the reaction temperature and stoichiometry, thereby reducing the inherent hazard and long addition time.

The reaction between **1** and ethyl acrylate in anhydrous toluene with 10 mol % TFA was used to survey various reaction temperatures and flow rates in a Vapourtec™ R2+/R4[18a] flow reactor, as it had the most immediate relevance to a project in progress (Fig. 2). The reaction set-up was very simple. Compound **1** (2.4 mmol, 1.2 equiv, 1.2 M in solvent) was introduced into a 2 ml loading loop, and a mixture of ethyl acrylate (2.0 mmol, 1 equiv, 1 M in solvent) and TFA (0.1 equiv) was introduced into another. The solutions were pumped at equal rates through the mixing T-piece into 2 × 10 ml heated reactor loops linked in series. The tubing was perfluoroalkoxyethylene of 1 mm internal diameter throughout. The reaction mixture was collected in a flask containing aqueous $NaHCO_3$ to neutralise the acid. The product was extracted into methyl *tert*-butyl ether, washed with brine, dried and concentrated. The yield and purity of the product were estimated by ^1H NMR spectroscopy by using a standard solution of *sym*-trioxane in $CDCl_3$. Isolated yield refers to the yield following purification by flash chromatography, however, for the initial survey we used calculated yields.

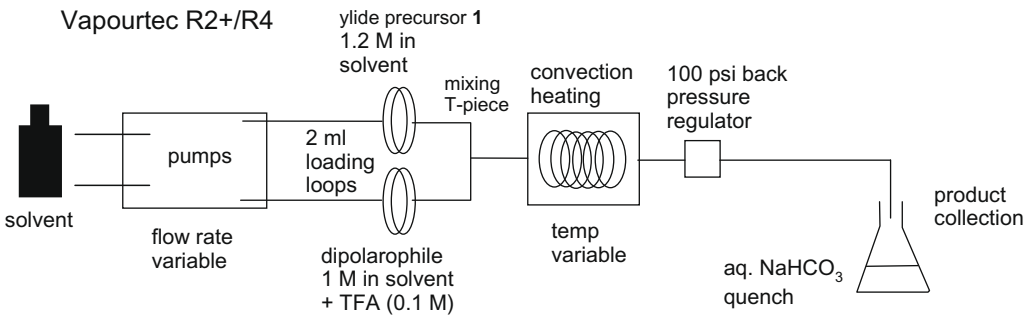
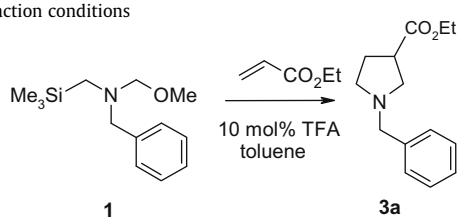


Figure 2. Schematic apparatus set-up for conducting [3+2] cycloaddition reactions using the Vapourtec R2+/R4 reactor.

Table 1
Survey of reaction conditions



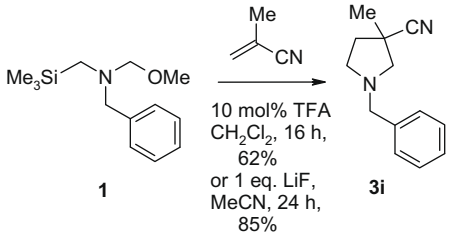
1 3a

Entry	Residence time (min)	Temp (°C)	Calcd yield [a] (%)	Isolated yield[b] (%)
1	60	20	89	
2	30	20	74	
3	60	70	99	
4	30	70	93	
5	10	70	89	83
6	30	100	93	
7	15	100	86	
8	5	100	54	

[a] From the ^{1}H NMR spectrum of the crude product, *sym*-trioxane internal standard.
[b] After flash chromatography.

The flow rate was varied to give a residence time from 5 to 60 min, and a temperature range between 20–100 °C with a typical operating pressure of 7–9 bar. The overall reagent concentration was kept at 0.5 M. The results are shown in Table 1.

The reaction proceeded at room temperature (entries 1 and 2), with a lower yield of product under a shorter residence time. This was to be expected, as Achiwa et al.[21] performed similar cycloadditions at 0–20 °C for 3 h to obtain high yields. From heated reactions (entries 3–7), we found that the yields of **3a** were good at



1 3i

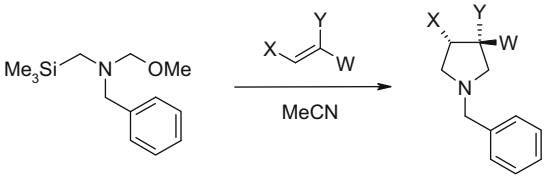
Scheme 2. Batch synthesis of **3i.**

70–100 °C, with a slight trend to better yields with longer residence times. Even with a residence time as short as 10 min at 70 °C (entry 5), the yield was satisfactory, although with only 5 min residence time at 100 °C (entry 8), it was significantly lower.

As we wanted to maximise product throughput, we subsequently focussed on heated reactions with a fast flow rate. Some of the reactions were repeated with dichloromethane and acetonitrile as solvents, though the former could not be pumped satisfactorily. Since the yields were marginally better with acetonitrile (Table 2, entry 1), this solvent was used in further experiments with other dipolarophiles.

The more reactive (and therefore more potentially hazardous) dipolarophiles, such as diethyl fumarate, diethyl maleate and *N*-methylmaleimide (Table 2, entries 2–4) gave high yields (>80%) under the same conditions as ethyl acrylate (entry 1, 10 min, 70 °C). Other diploarophiles that gave good yields (>65%) were (*E*)-ethyl cinnamate, (*E*)-2-nitrostyrene and ethyl 4,4,4-trifluorocrotonate (entries 9, 14 and 15). Yields were more modest (39–56%) with ethyl crotonate, ethyl methacrylate, crotononitrile and methacrylonitrile (entries 5, 7, 10 and 12). In an attempt to im-

Table 2
Cycloaddition reactions of **1** with various dipolarophiles in acetonitrile



1 3a-l

Entry	Dipolarophile	Product	W	X	Y	Reaction time (min)	Temp (°C)	Calculated yield[a] (%)	Isolated yield[b] (%)	Ref.
1	Ethyl acrylate	**3a**	CO_2Et	H	H	10	70	92	85	11e,12
2	Diethyl fumarate	**3b**	CO_2Et	CO_2Et	H	10	70	98	85	19
3	Diethyl maleate	**3c**	H	CO_2Et	CO_2Et	10	70	89	83	19
4	*N*-Methylmaleimide	**3d**	H	CON(Me)CO		10	70	86	81	20
5	(*E*)-Ethyl crotonate	**3e**	CO_2Et	Me	H	10	70	59	52	21
6						30	70	52	ND[c]	
7	Ethyl methacrylate	**3f**	CO_2Et	H	Me	10	70	37	42	[d]
8						10	100	62	63	
9	(*E*)-Ethyl cinnamate	**3g**	CO_2Et	Ph	H	10	70	72	65	22
10	(*E*)-Crotononitrile	**3h**	CN	Me	H	10	70	34	39	23
11						10	100	62	59[e]	
12	Methacrylonitrile	**3i**	CN	H	Me	10	70	56	71[e]	24
13						30	70	28	ND[c]	
14	(*E*)-2-Nitrostyrene	**3j**	NO_2	Ph	H	10	70	82	77	25
15	(*E*)-Ethyl 4,4,4-trifluorocrotonate	**3k**	CO_2Et	CF_3	H	10	70	79	74	26
16	(*E*)-Ethyl 4-bromocrotonate	**3l**	CO_2Et	CH_2Br	H	10	70	85	56	[d]

[a] From the ^{1}H NMR spectrum of the crude product, *sym*-trioxane internal standard, accurate to ±3% as samples weighed to nearest 0.1 mg (the accuracy of the calculated yields was limited by the accuracy of weighing the NMR samples, hence in entries 7, 8 and 10 they appear marginally greater than the isolated yields).
[b] After flash chromatography, purity >95% unless stated otherwise.
[c] ND = not determined.
[d] Novel compounds were characterised by spectroscopic means.
[e] Purity <90% due to the presence of decomposition products of the azomethine ylide precursor.

prove some of the yields, the residence time was increased or a higher temperature was employed. This sometimes increased the yield as in the cases of ethyl methacrylate (entries 7 and 8) and crotononitrile (entries 10 and 11), but not with ethyl crotonate (entries 5 and 6) and methacrylonitrile (entries 12 and 13). Methacrylonitrile (entry 12) gave a relatively high mass recovery after chromatography, but this was due to impurities.

For comparison, the reaction of **1** with methacrylonitrile under batch conditions in acetonitrile was conducted with TFA and LiF at room temperature (Scheme 2).

The yield of the TFA-catalysed reaction in batch mode was slightly superior to the corresponding heated reaction in flow (entry 12) and purification of the product was less difficult. Under LiF-promoted conditions, the yield was even higher, suggesting that the slow rate of generation of the azomethine ylide increases trapping efficiency. However, owing to the insolubility of LiF, these conditions are unsuitable for flow, but the reactions also present less of a hazard as there was no noticeable exotherm.

To demonstrate the viability of performing the cycloaddition in flow on a reasonable scale, the Vapourtec™ R2+/R4 was equipped with four heated reaction loops (total volume 40 ml) so that we could react compound **1** with ethyl acrylate under the previously optimised conditions (0.5 M overall in MeCN, 70 °C, 10 min). From a reaction on 30 g scale, we obtained compound **3a** in 87% yield, after chromatography in only 1 h.

We have described the feasibility of a potentially hazardous cycloaddition reaction under conditions of continuous flow. After optimisation, uniformly high yields of cycloadducts were obtained for certain reactive electron-deficient alkenes, and a multi-gram synthesis was demonstrated for compound **3a**. For less reactive dipolarophiles such as methacrylonitrile, lithium fluoride-promoted batch conditions are probably preferable.

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