DDT Vol. 8, No. 13 July 2003

Continuous flow reactors for drug discovery

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To develop a new generation of drugs, pharmaceutical companies need to be able to synthesize and screen novel chemicals with enhanced speed. New technology that would enable a cost-neutral increase in the number of potential drug candidates would provide a distinct competitive advantage. The miniaturisation of chemical reactors offers many fundamental and practical advantages of relevance to the pharmaceutical industry, which is constantly searching for controllable, information-rich, high-throughput and environmentally friendly methods of producing compounds with a high degree of chemical selectivity. This article reviews the current and future applications of micro reactors that could enhance the drug discovery process.

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The success of pharmaceutical companies resides largely on their ability to synthesize novel chemical entities (NCEs) and to optimize the production of marketable drugs. In an industry where development costs are extraordinarily high, it is important to develop new technology that enables the rapid synthesis and screening of NCEs. The miniaturization of chemical reactors offer many advantages of relevance to the pharmaceutical industry, which is constantly searching for high-throughput methods of producing products with a high degree of chemical selectivity [1–8]. This review illustrates how miniaturization of chemical reactors could revolutionize medicinal chemistry and the pharmaceutical industry through the implementation of innovative technology.

In their simplest form, micro reactors consist of a network of micron-sized channels (10–300 μm in diameter) etched into a solid substrate. Several materials, such as silicon, quartz, glass, metals and polymers, have been used to construct micro reactors [9]. Important considerations when choosing a material include chemical compatibility, the ease and reproducibility of fabrication, whether the material supports electroosmotic flow (EOF) [10–13] with the solvents of interest and compatibility with detection methods. Glass is a popular choice because it allows EOF with many common solvents, it is chemically inert, it enables the use of a range of visible-light detection methods and the fabrication techniques are well established. Depending on the material used, a range of fabrication methods, such as photolithography, hot embossing, powder blasting, injection moulding and laser micro-forming, where the channels are etched into the material using high-powered lasers, are available [9,14]. For glass micro reactors, which are ideal for synthetic chemistry, photolithographic fabrication of the channel network is performed [15,16].

For solution-based chemistry, the channel networks are connected to a series of reservoirs containing chemical reagents to form the complete device with overall dimensions of a few cm. In the micro reactor, reagents can be brought together in a specific sequence, mixed and allowed to react for a specified time in a controlled region of the channel network using electrokinetic or hydrodynamic pumping. For electrokinetically driven systems, electrodes are located in the appropriate reservoirs (Fig. 1), which allows the sequential application of voltages under automated computer control. This control offers a simple but effective method of moving and separating reactants and products within a micro reactor, without the need for moving parts. Hydrodynamic pumping, by comparison, exploits conventional or micro-scale pumps, notably syringe-type pumps, to manoeuver solutions around the channel network.

Until recently, the greatest research effort in the field of micro-scale devices has been in analytical science. One of the main aims of this research is to develop a so-called miniaturized

PII: S1359-6446(03)02732-6

Abbreviations

Boc:	*tert*-butoxycarbonyl
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC:	*N,N*-Dicyclohexylcarbodiimide
Dmab:	4-[*N*-(1-(4,4-dimethyl-2,6-diococyclohexylidene)-3-methylbutyl)amino]benzyl
DMF:	*N,N*-Dimethylformamide
EDDA:	Ethylenediamine acetate
EtOAc:	Ethyl acetate
EtOH:	Ethanol
Fmoc:	9-Fluorenylmethoxycarbonyl
MeOH:	Methanol
$NaNO_2$:	Sodium nitrite
NaOMe:	Sodium methoxide
NMP:	*N*-Methyl-2-pyrrolidinone
$^iPr_2EtN$:	Diisopropylethylamine
TBAF:	tetra-*n*-butylammonium fluoride
THF:	Tetrahydrofuran
TMS:	Trimethylsilyl

total analytical system (μ–TAS) [17–24]. To date, the most popular area of μ-TAS research has been in the biomedical field, particularly in genomics and proteomics, where it has been used in the analysis of both DNA and proteins [25–32] and has resulted in the release of several commercial devices. Alongside the continuing development of μ-TAS, a concerted effort has been underway to establish the benefits that micro reactors can bring to the field of reaction chemistry. The ability to manipulate reagent concentrations in both space and time by electrokinetic voltage control within the channel network of a micro reactor provides a level of reaction control that is not attainable in bulk-stirred reactors, where concentrations are generally uniform. Many chemical reactions have been demonstrated to show improved reactivity, product yield and selectivity when performed in micro reactors, compared with those generated using conventional laboratory practices.

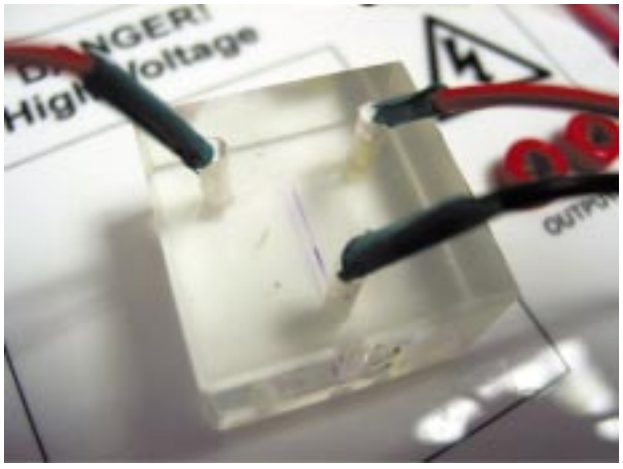


Figure 1. Reaction in process within a micro reactor under electroosmotic flow (EOF) control. The platinum electrodes in the reservoirs are used to apply voltages to the reagents, which are placed within the reservoirs. The product is collected in the final reservoir, which contain a ground electrode.

The outcome of the reported research has confirmed that micro reactor methodology is applicable to performing both gas and liquid-phase reaction chemistry [33]. The evidence is that the unique *modus operandi* of micro reactors, namely the low-volume spatial and temporal control of reactants and products in a diffusive mixing environment, in which distinctive thermal and concentration gradients exist, offers a novel method for chemical manipulation and generation of products. In short, micro reactors are new tools with which to generate molecules and to increase our knowledge of complex chemical processes. When compared with the equivalent bulk reactions, reactions performed in a micro reactor invariably generate purer products in a higher yield and in much shorter times. Therefore, one of the obvious applications is in drug and process discovery, where the generation of compounds, either with different reagents or under variable conditions, is an essential factor.

Performing chemical reactions within a microfluidic system also provides the opportunity to perform real-time separations. Therefore, integration of a micro reactor device, via a purification step, with one of the many highly sensitive microchannel-based biological assay systems would provide a drug discovery tool. This level of integrated functionality within one device clearly addresses some of the pharmaceutical industry's requirements for rapid compound production and screening (Fig. 2). Apart from the greatly reduced reaction times demonstrated for the micro reactors, handling times and assay and chemical reagent costs are virtually eliminated with this proposed technology.

Chemical reactions performed in micro reactors

To date the majority of reactions that have been performed in micro reactors have been single-step processes, conducted simply to demonstrate that it is possible to perform chemical synthesis within such devices. A summary of the reactions that have been performed in micro reactors is presented in Table 1 and these are reviewed in detail in ref [33].

To prepare compounds that are of interest to the pharmaceutical industry it is important to demonstrate that multi-step reactions may be performed within such devices. In addition, it is imperative to demonstrate that by using different reagents as the starting materials, combinatorial

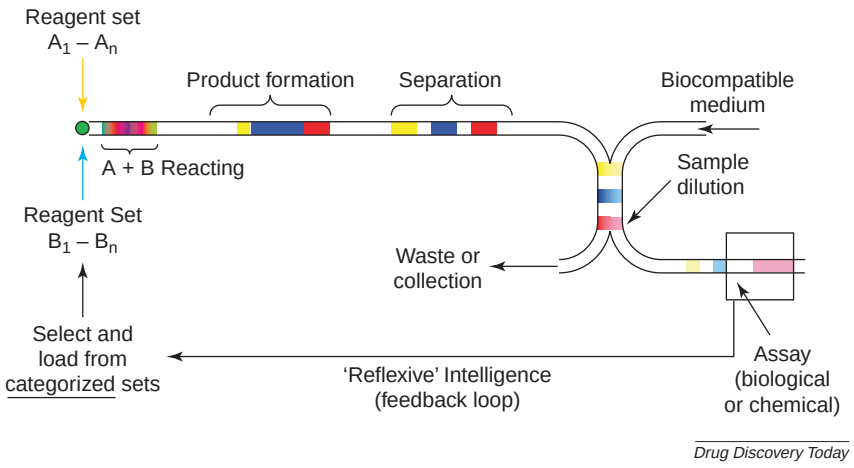


Figure 2. The micro reactor may be used to produce a combinatorial library of compounds, which may be separated by integrating the micro reactor with either a HPLC or capillary electrophoresis system, for example. The end of the separation column may be further integrated to a bioassay system such that each compound can be individually screened.

libraries of compounds can be rapidly generated. A summary of the reactions performed in micro reactors that meet these criteria is reviewed in detail below.

Combinatorial synthesis in micro reactors

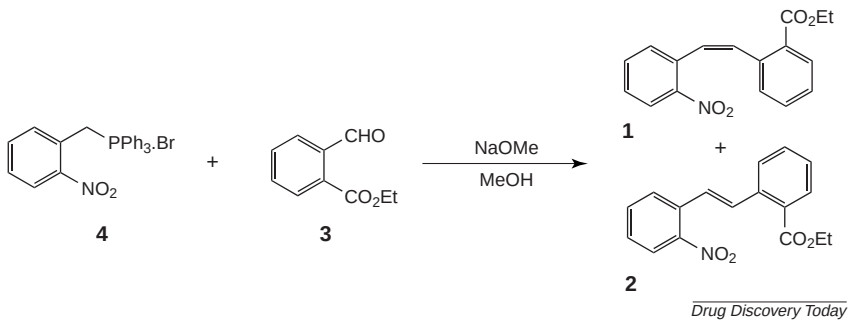
Wittig reactions

Skelton and colleagues have reported the application of micro reactors to the Wittig reaction [34,35]. The authors used the micro reactor to prepare the *cis*- and *trans*-nitrostilbene esters **1** and **2** via this reaction (Scheme 1). Several features, such as stoichiometry and stereochemistry, were investigated. When two equivalents of the aldehyde **3** to the phosphonium salt **4** were used in the reaction, a conversion of 70% was achieved, which represented an increase in reaction efficiency of 10% over the traditional batch synthesis. The reaction stoichiometry was subsequently reduced to 1:1, but using continuous flow of the reagents, the conversion was only 39%. This was increased to 59% using an injection technique, where slugs of the phosphonium salt **4** were injected into a continuous flow of the aldehyde **3**. The research was further extended to investigate the stereochemistry of the reaction, where the ratio of isomers **1** and **2** was controlled by altering the voltages applied to the reagent reservoirs within the device, which in turn affected the EOF and electrophoretic mobility of the reagents. The variation in the external voltage subsequently altered the relative reagent concentrations within the device, producing *Z/E* ratios (the ratio of *cis*- and *trans*-isomers) in the region of 1:9. By comparison, when a traditional batch synthesis was performed using the same reaction time, concentration, solvent and stoichiometry, a *Z/E* ratio of approximately 3:1 was observed. This demonstrated that significant control was possible in a micro reactor compared

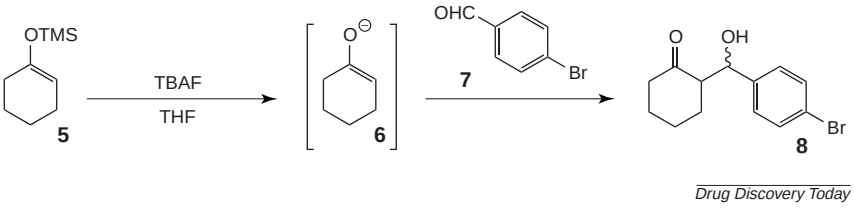
Table 1. Single step reactions performed in micro reactors

Reaction	Chip material	Solvent	Conversion (%)	Pumping mechanism	Ref
Suzuki	Glass	aq THF	67	EOF	[45]
Kumada coupling	Polypropylene	THF	60	Syringe pump	[46]
Nitration	Glass	benzene	65	EOF	[47]
Enamine formation	Glass	MeOH	42	EOF	[48]
Diazo coupling	Glass	MeOH	37	EOF	[49]
		MeCN	22		
Photocyanation	Polymer	pyrene/H_2O	73	Syringe pump	[50]
Dehydration	Glass/PDMS	EtOH	85–95	EOF or syringe pump	[51]
Esterification	Glass/PDMS	EtOH	30	Syringe pump	[52]
Photochemical	Silicon/quartz	$(CH_3)_2CHOH$	60	Syringe pump	[53]
Photochemical	Glass	MeOH	80	Syringe pump	[54]
Phase transfer	Glass	EtOAc	100	Syringe pump	[55]
Fluorination	Ni or Cu	Nitrogen gas	90–99	Syringe pump	[56,57]
Fluorination	Silicon/Pyrex	MeOH	80	Syringe pump	[58]
Oxidation	Al	none	75–99	Syringe pump	[59]

Abbreviations: EOF, electroosmotic flow; PDMS, polydimethylsiloxane; THF, tetrahydrofuran.



Scheme 1. Wittig reaction.



Scheme 2. Synthesis of β-hydroxyketones.

with batch reactions. The authors also demonstrated that the micro reactor could be used as a tool for rapid reaction development and optimization based on analogue chemistry by using different aldehydes in the reaction [35].

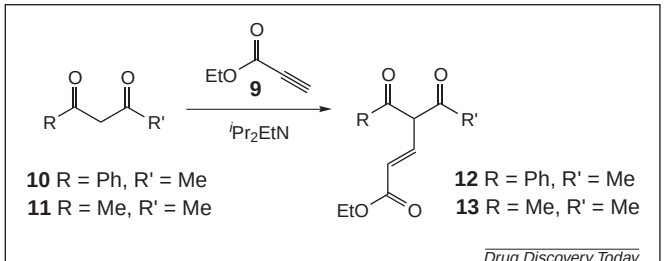
Carbanion chemistry

Carbanion chemistry is the most common method of C–C bond formation, however the temperature of such reactions often governs the stereochemistry of the product. Therefore, micro reactors have a considerable attraction because of their excellent temperature control. Wiles and colleagues have demonstrated the use of silyl enol ethers in the aldol reaction within a micro reactor [36] where quantitative conversion of the silyl enol ethers to β-hydroxyketones was observed in 20 min in the micro reactor, compared with traditional batch systems where quantitative yields were only obtained when extended reaction times of up to 24 h were employed. One example involved the treatment of trimethylsilyl (TMS) enol ether **5** with tetra-*n*-butylammonium fluoride (TBAF), to generate the tetra-*n*-butylammonium enolate **6** *in situ*, followed by condensation with *p*-bromobenzaldehyde **7** to give the β-hydroxyketone **8** in a 100% conversion (Scheme 2). The reaction was successfully performed using a variety of other silyl enol ethers and aldehydes, which demonstrates that micro reactors can be used in the rapid synthesis of combinatorial libraries.

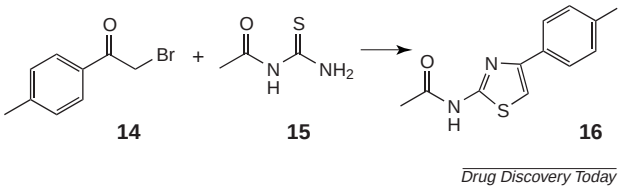
Wiles and co-workers [37] have also reported the preparation of the enolates from a series of 1,3-diketones using an organic base and their subsequent reaction with a variety of Michael acceptors, such as **9**, to afford 1,4-addition products within a micro reactor (Scheme 3). When using a continuous flow of the reagents **9** and **10**, 15% conversion to the product **12** was observed, compared with 56% when the diketone **11** was reacted with **9** forming the Michael adduct **13**. The authors demonstrated enhancements in the conversions through the application of the stopped-flow technique. This procedure involved the mobilization of reagents through the device for a designated period of time, using an applied field before the flow was subsequently paused by the removal of the applied field, before re-application of the field. Using the regime of 2.5 s on and 5 s off, the conversion to **12** was improved to 34%, whereas lengthening the stopped-flow period to 10 s resulted in a further increase to 100%. This was compared with the preparation of **13**, in which the regime of 2.5 s on and 5 s off resulted in an increase in conversion to 95%. This demonstrated that the enolate of 2,4-pentanedione **11** was more reactive than the corresponding enolate of benzoyl acetone **10**. The authors propose that the observed increase in conversion when using the technique of stopped-flow was due to an effective increase in residence time within the device corresponding to the different kinetics associated with these reactions.

Hantzcsh reactions

Special equipment is required when performing large-scale reactions at elevated temperature. However, the synthesis of a series of 2-aminothiazoles using a Hantzsch reaction within a micro reactor has been demonstrated [38]. During the experiments, the T-shaped micro reactor was heated to



Scheme 3. Michael addition.



Scheme 4. Hantzsch synthesis of thiazoles.

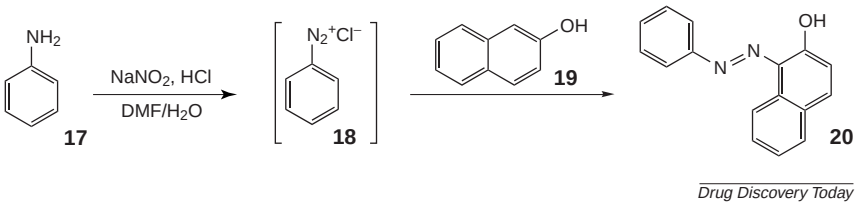
70°C using a Peltier heater, which was aligned with the channels and the heat generated by the device was applied to the base of the micro reactor. The reaction of α-bromoketone **14** with the thiourea derivative **15**, using *N*-methyl-2-pyrrolidinone (NMP) as solvent, resulted in the preparation of aminothiazole **16** in a 85% conversion (Scheme 4). A range of aminothiazole derivatives were prepared using alternative α-bromoketones as starting materials.

Whereas the above examples represent sequential combinatorial synthesis, Kikutani and co-workers have recently reported an example of parallel synthesis within a micro reactor [39]. The authors used their micro reactor to synthesize a range of amides, by reaction of a selection of amines with a diverse range of acid chlorides via a phase transfer reaction.

Multi-step synthesis in micro reactors

Diazotization reactions

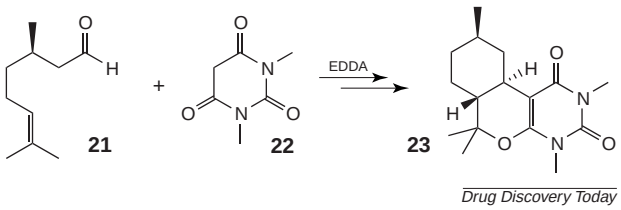
Diazotization of aromatic amines is an industrially important yet dangerous process. The explosive nature of diazonium salts necessitates extreme care in reaction processing. Therefore, the small volume of micro reactors affords a safe route to perform hazardous reactions. Wootton and colleagues [40] have demonstrated the synthesis of azo compounds using hydrodynamic pumping within a micro reactor. The authors demonstrated that aniline **17** could be converted into the diazonium salt **18** before being reacted *in situ* with β-naphthol **19** to form the azo dye **20** in up to a 52% overall conversion (Scheme 5). The ability to prepare and react diazonium salts *in situ* clearly demonstates the versatility of micro reactor technology.



Scheme 5. Synthesis of azo dyes via diazotization.

Condensation reactions

The synthesis of cycloadducts in a micro reactor using hydrodynamic-driven flow has been reported [41]. The reaction consisted of Knoevenagel condensation of an aldehyde **21** with a 1,3-diketone **22** in the presence of ethylenediamine acetate (EDDA) as catalyst, using aqueous methanol as a solvent. The reaction intermediate underwent a spontaneous intramolecular hetero-Diels-Alder reaction to form cycloadduct **23** in a 60–68% conversion (Scheme 6).



Scheme 6. Cycloadduct formation.

Peptide synthesis

Watts and co-workers have recently demonstrated multi-step synthesis of peptides in a micro reactor [42,43]. The authors evaluated the reactor using a carbodiimide coupling reaction of Fmoc-β-alanine **24** with the amine **25** to give the dipeptide **26** in up to 93% conversion (Scheme 7).

The authors also demonstrated that the dipeptide could be prepared from pre-activated carboxylic acids [42,43]. The reaction of the pentafluorophenyl (PFP) ester of Fmoc-β-alanine **27** with amine **25** gave a 100% yield of dipeptide **26** in 20 min (Scheme 8). This represented a significant increase in yield compared with the traditional batch synthesis, where only a 50% yield was obtained in 24 h.

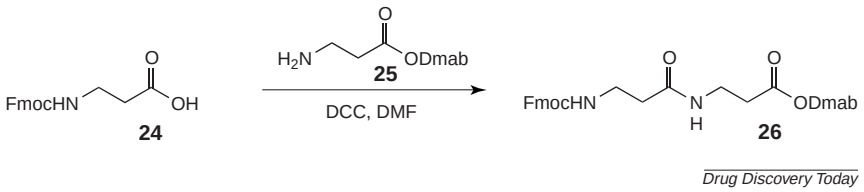
Having demonstrated that peptide bonds could be successfully formed when using a micro reactor, the authors then found that they could extend the methodology to the preparation of longer chain peptides. Using the micro reactor, the 4-[*N*-(1-(4,4-dimethyl-2,6-diococyclohexylidene)-3-methylbutyl)amino]benzyl (Dmab) ester of Fmoc-β-alanine **28** was reacted with one equivalent of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) to give the free amine **25** in a quantitative conversion. The authors then reacted the amine *in situ* with the pentafluorophenyl ester **29** to give the dipeptide **30** (Scheme 9) in a 96% overall conversion.

Having shown that more complex peptides could be produced by removal of the *N*-protecting group, the authors then demonstrated that they could remove the Dmab ester using hydrazine.

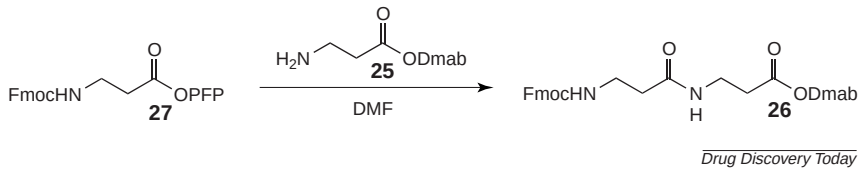
The reaction of the Dmab ester **28** with one equivalent of hydrazine resulted in quantitative deprotection, producing the carboxylic acid **24** (Scheme 10). Solid phase peptide synthesis, by comparison, generally requires 2% hydrazine in *N*,*N*-dimethylformamide (DMF) to effect complete deprotection.

Watts and co-workers have further extended this approach to the synthesis of tripeptide **32** [58]. The reaction of pentafluorophenyl ester **27** with amine **25** formed dipeptide **26**, which was reacted with DBU to effect 9-fluorenylmethoxycarbonyl (Fmoc) deprotection. The amine **31** was then reacted *in situ* with another equivalent of pentafluorophenyl ester **27** to prepare tripeptide **32** in a 30% overall conversion (Scheme 11). This approach clearly demonstrates that intermediates can be generated *in situ* and used in subsequent reactions, thus enabling the combinatorial synthesis of peptides, which are of biological and pharmaceutical interest.

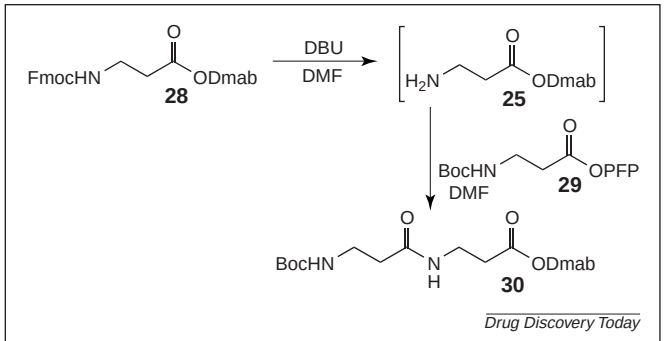
These same authors then investigated racemization in peptides derived from α-amino acids [44]. The reaction of the pentafluorophenyl ester of *R*-2-phenylbutyric acid **33** with α-methylbenzylamine **34**, gave the amide **35** in quantitative conversion with 4.2% racemization (Scheme 12). Importantly, there was less racemization than was observed in the batch reaction at the same concentration and temperature. The reduced level of racemization was attributed to the reduced reaction times observed within the micro reactors. This demonstrates that there would be significant advantages to performing such reactions in micro reactors compared with traditional batch systems.



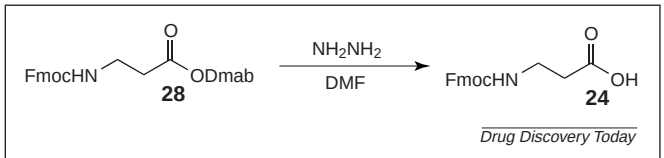
Scheme 7. Dipeptide formation.



Scheme 8. Dipeptide formation.



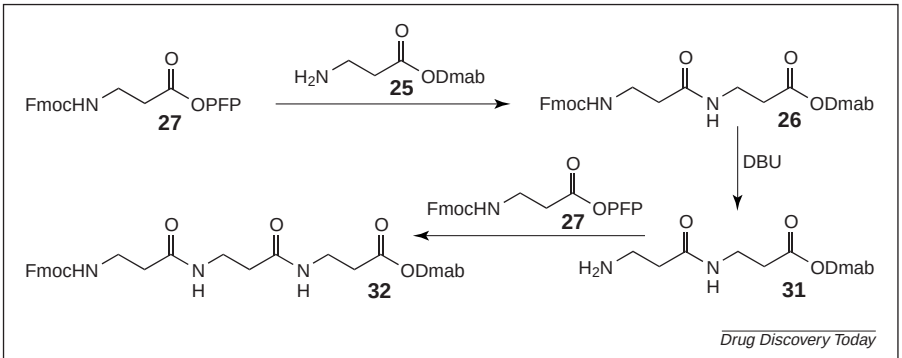
Scheme 9. Multi-step dipeptide formation.



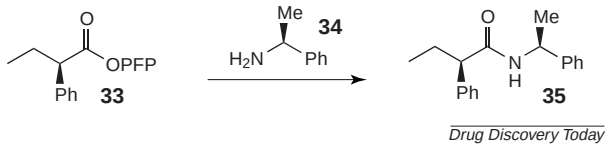
Scheme 10. Deprotection to produce carboxylic acids.

Conclusions

Micro reactor chemistry is currently showing great promise as a novel method on which to build new chemical technology and processes. Reactions performed in micro reactors invariably generate pure products in a high yield, in shorter periods of time than the equivalent batch reactions and in sufficient quantities to perform full characterization. Therefore, one of the obvious applications is in combinatorial chemistry and drug discovery, where the generation of compounds with either different reagents or under variable



Scheme 11. Tripeptide formation.



Scheme 12. Peptide racemization.

conditions is an essential factor. In short, micro reactor technology has the potential to revolutionize the pharmaceutical industry because the number of potential drug candidates that can be prepared and screened can be considerably increased, hence the likelihood of developing new drugs is considerably enhanced.

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