CHEMTRIX
Scalable Flow Chemistry

Application Note 17

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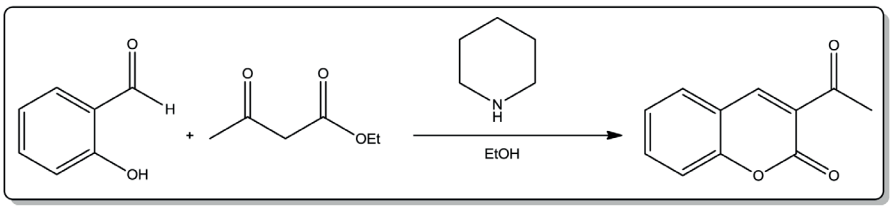
Chemtrix BV

Application Note 17: 13,000 x Scale-up of 3-Acetylcoumarin –Demonstration of Scalable Flow Synthesis; from R&D to Production without Parameter Re-optimisation



Introduction: With a large number of natural products bearing a 2*H*-1-benzopyran-2-one heterocyclic core (Figure 1), coumarins have been shown to posses anticoagulant, antidiabetic and antibiotic properties, it is however the antioxidant and anti-proliferative effects that stand out for this class of biologically active compounds.[1] In addition to their pharmaceutical application, coumarins are also utilised as brightening agents,[2] laser dyes,[3] as photovoltaic sensitisers, in consumer products such as fragrances and cosmetics,[4] and as antifungal agents in agrochemicals.[5]

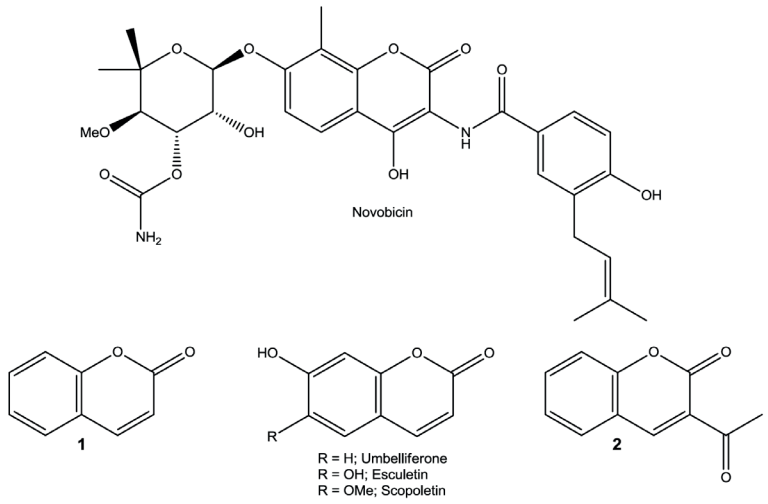
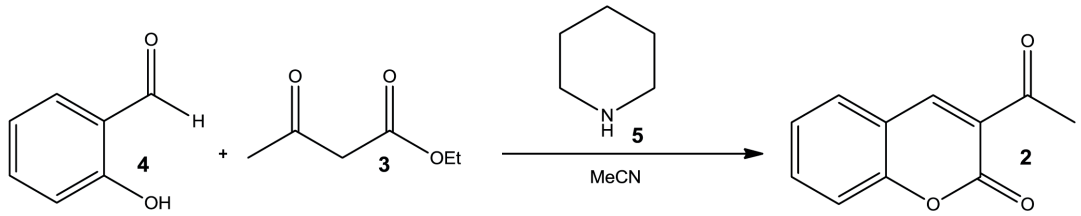


Figure 1. A selection of natural and synthetic coumarin **1** derivatives.

The synthesis of coumarins can be achieved using several named reactions including the Claisen re-arrangement, Perkin reaction and the Pechmann reaction; herein we examine the synthesis of 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2** (3-acetylcoumarin)), *via* the Knoevenagel condensation of ethyl acetoacetate **3** and 2-hydroxybenzaldehyde **4** in the presence of catalytic piperidine **5** (Scheme 1). Owing to the use of this heterocycle **2** as a product, reagent[6,7] and ligand,[8] it was decided to develop methodology for its efficient production under continuous flow conditions.

By utilising the scalable technology platform of Labtrix® micro reactors and KiloFlow® meso reactors, we are able to demonstrate the development of synthetic methodology on the mg-scale and subsequently translate the reaction parameters to a meso-flow reactor for the large-scale material production without the need to perform any re-optimisation of the reaction conditions.[9]

Figure 2 illustrates the commercially available turn-key instruments that form the basis of this technology platform; Labtrix®-S1 (top right) an automated reaction screening tool, Labtrix® Start (top left) a manual screening platform and KiloFlow® (bottom) the continuous flow production unit that fits in a standard fume cupboard.



Scheme 1. Synthetic route selected for the continuous flow synthesis of 1-(2-methyl-2*H*-chromen-3-yl) ethanone **2**.

Figure 2. Photographs illustrating the scalable flow chemistry platform of Chemtrix BV (top left) Labtrix® S1, (top right) Labtrix® Start and (bottom) KiloFlow®.

Materials Used: Unless otherwise stated, all reaction and wash solvents were of HPLC grade and used as received (Fisher Scientific, UK). 2-Hydroxybenzaldehyde (99 %) and piperidine (99 % extra pure) were obtained from Acros Organics (Belgium) and ethyl acetoacetate (99 %) was sourced from Aldrich (UK).

Instrumentation: Analytical assessment of the flow reactions was performed using a Varian GC-FID (calibrated for product **2** vs. 2-hydroxybenzaldehdye **4**) fitted with a CP-Sil (30 m (long) x 0.25 mm (o.d.) x 0.25 µm (film thickness); Phenomenex, UK) column. Employing a Helium flow rate of 1.6 ml min^{-1} (99.9999 %; Energas, UK) and a thermal program utilising an intial oven temperature of 50 ºC (0 min hold) ramping to 240 ºC at 40 ºC min^{-1} (0 min hold) then to 300 ºC at 100 ºC min^{-1} (3.0 min hold), retention times of ethyl acetoacetate **3** = 2.49 min, 2-hydroxybenzaldehyde **4** = 2.92 min and1-)2-methyl-2*H*-chromen-3-yl) ethanone **2** = 5.18 min were obtained.

Product purity was assessed by NMR spectroscopy with ^{1}H and ^{13}C NMR spectra obtained at room temperature as solutions in deuterated dimethylsulfoxide (*d*-DMSO). The spectra were recorded using a Jeol GX400 spectrometer and all spectral data compared with the literature. Mass spectra were recorded as solutions in EtOH using an Agilent 6890 Series GC-MS fitted with a HB-1 column (0.20 mm (o.d.) x 0.33 µm (film thickness) x 12 m (length)) employing a helium flow rate of 1.0 ml min^{-1} and a thermal program of 50 ºC (1 min hold) ramping to 320 ºC at 30 ºC min^{-1} (5 min hold). The collected mass spectra were subsequently compared with the NIST 02 database.

At the lab-scale, flow reactions were performed in a standard PEEK Labtrix® Start system fitted with a 3221 or 3223 device (Volume = 1 or 10 µl) and at the pilot scale, reactions were performed in a PEEK KiloFlow® Basic system which comprised of two pump modules with bottle pressurisation (0.5 bar N_2), a PEEK holder containing 2 x heat exchangers for reagent pre-heating, 2 x reactors for mixing and reaction (Total volume = 13.0 ml) and one water-cooled heat exchanger to cool the reaction products to room temperature ahead of collection. The holder was fitted with 17 bar pressure safety relief valves, a 7 bar BPR (Upchurch Scientific) and thermally regulated using a thermostat (Lauda, XT 150) and Kryo 55 thermal fluid.

Labtrix® Reaction Screening: Employing a solution of 2-hydroxybenzaldehyde **4** and ethylacetoacetate **3** in MeCN (1.00 and 1.05 M respectively) and a solution of piperidine **5** (0.05 to 0.4 M) in MeCN, the effect of reaction time and temperature was screened for the synthesis of 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2**. In order to ensure that the data collected was of a high quality and representative of reactions taking place within the micro reactor, a solution of HCl in NMP (1.0 M) was employed as the quench; allowing assessment of reaction time (30, 45 and 60 s), temperature (25 to 150 ºC) and base equivalents (0.05, 0.1, 0.2 and 0.4). Reactions were performed using Labtrix® Start fitted with device 3221 (1 µl with SOR-2 mixer) as illustrated in Figure 3.

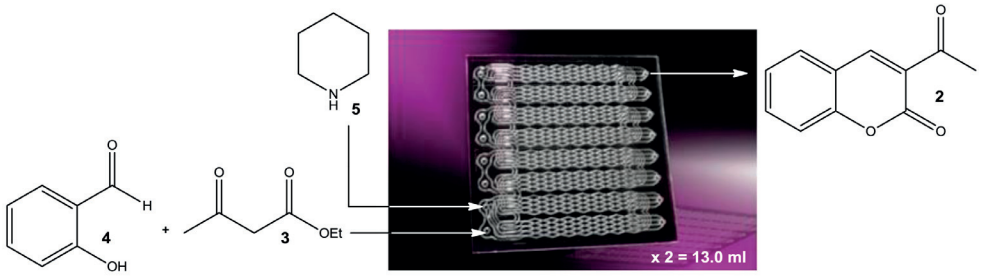


Figure 3. Schematic illustrating the reaction manifold assessed for the synthesis of 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2**.

As Figure 4 illustrates, the optimal conditions were found to be 0.4 M piperidine **4** a reaction time of 60 s and a system temperature of 125 ºC affording quantitative conversion of 2-hydroxybenzaldehyde **4** to 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2**. Under these optimal conditions, the reaction was performed in a 10 µl device (3223) in order to prepare sufficient material for full characterisation and structural confirmation; in the absence of a quench, 112 mg (99.2 % yield) of coumarin **2** was synthesised in 2 h. Analysis by NMR and GC-MS confirmed the product formed to be analytically pure 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2**. Over the assessment period, no crystallisation was observed in the reactor, collection tube or collection vessel confirming suitability for translation to KiloFlow®.

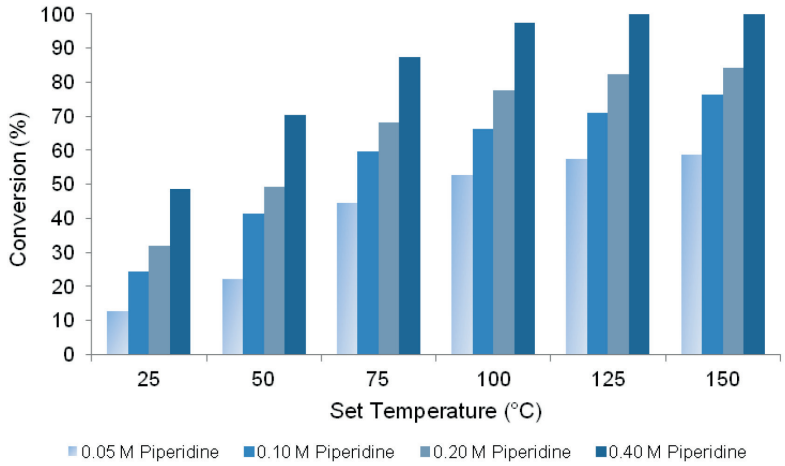


Figure 4. Summary of the results obtained in Labtrix® Start for the model reaction using MeCN as the reaction solvent.

Material Production: Operating KiloFlow® Basic (Reactor Volume = 13.0 ml) at a set flow rate of 6.5 ml min^{-1} (Total flow rate = 13.0 ml min^{-1}), a set temperature of 125 ºC, with water cooling of the reaction products, the condensation reaction was performed at scale utilising a solution of 2-hydroxybenzaldehyde **4**/ethyl acetoacetate **3** (1.0 M and 1.05 M respectively) with piperidine (0.4 M); Figure 5 illustrates the KiloFlow® Basic reactor manifold employed.

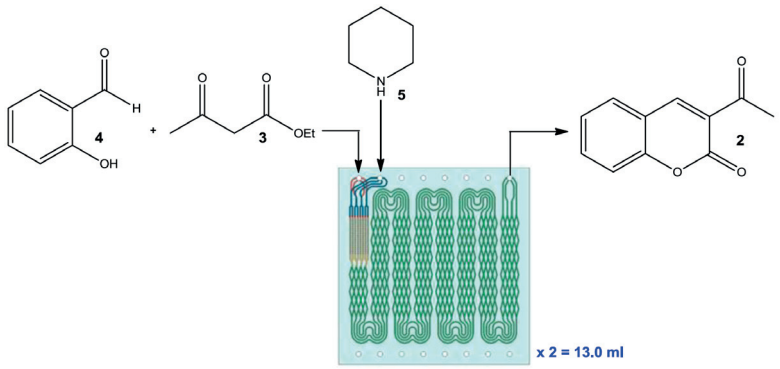


Figure 5. Schematic illustrating the reactor set-up used for the synthesis of 1-(2-methyl-2*H*-chromen-3-yl)ethanone **2** in KiloFlow® Basic.

Initially the system was filled with MeCN and thermally regulated at the desired reaction temperature of 125 ºC, after 15 min the wash solvent was replaced with the reactant solvents and after an additional 15 min, the reactor output stream was diverted from waste to collection. Figure 6 illustrates the yellow product **2** forming as the pre-heated reagent solutions exit the heat exchangers (HE) and meet in the first reactor where they are mixed then pass into a second reactor where they are given sufficient residence time to convert. Over a period of ~ 5 h, 4 litres of reaction product were collected volumetrically after which point the reactor was flushed with MeCN and cooled prior to stopping pumping.

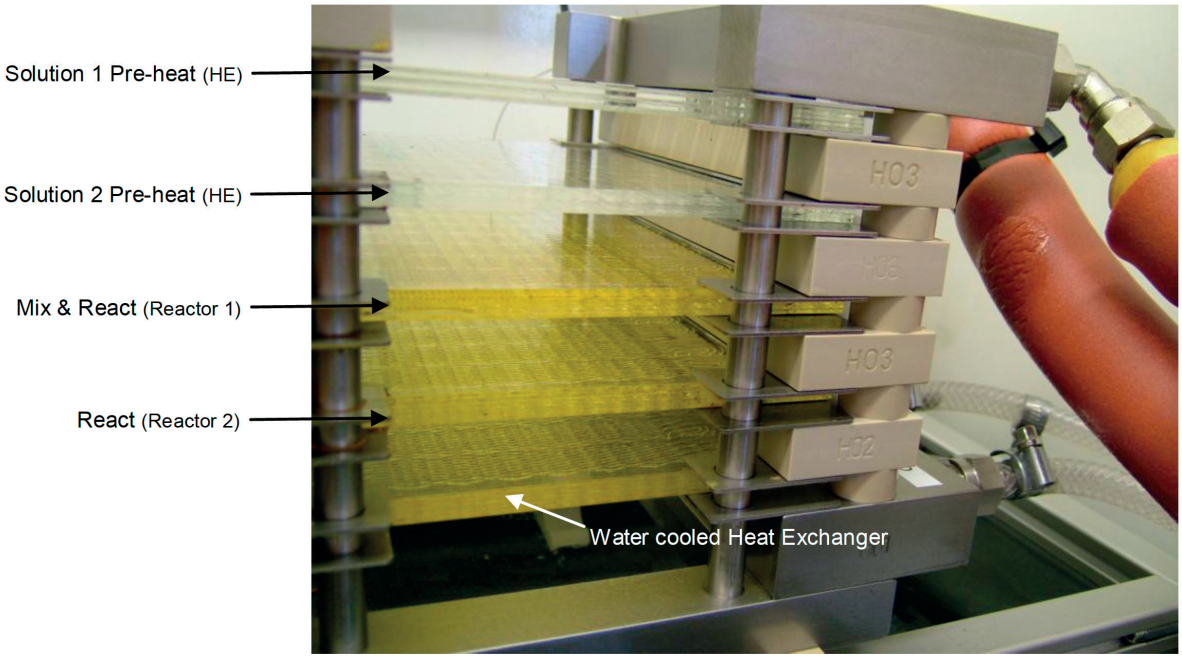


Figure 6. Illustration of the coumarin condensation reaction performed in KiloFlow® Basic using MeCN as the reaction solvent.

The reaction mixture was concentrated *in vacuo* and the organic residue dissolved in DCM and washed with aq. ammonium chloride. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a pale yellow solid (369.59 g, 98.18 % yield); Figure 7 illustrates the products isolated from Labtrix® (left) and KiloFlow® (right) respectively.

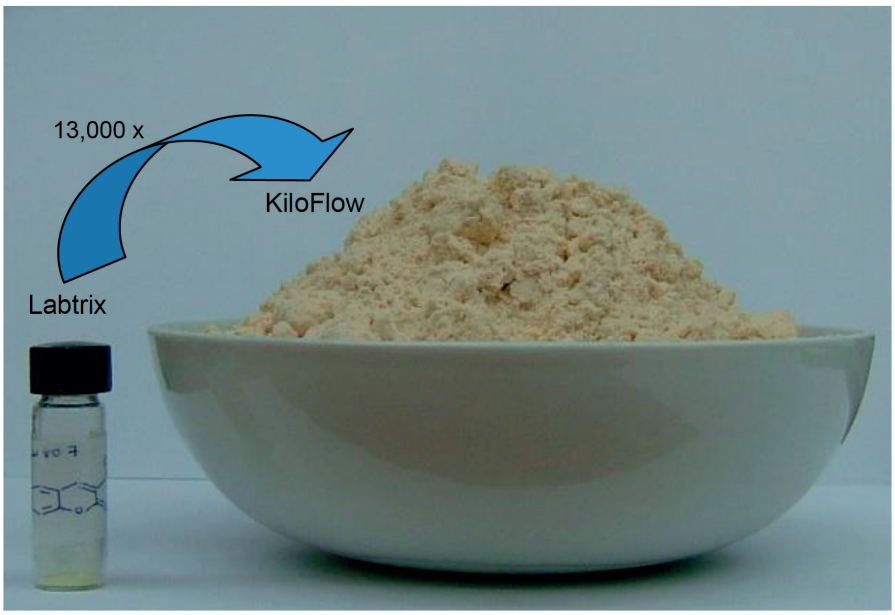


Figure 7. Photograph illustrating the coumarin product **2** synthesised in Labtrix® and KiloFlow® Basic.

Product Characterisation: Using NMR and mass spectrometry, the product purity was assessed and the ^{1}H NMR spectra obtained shown in Figure 8, with the aromatic region zoomed expand for clarity.

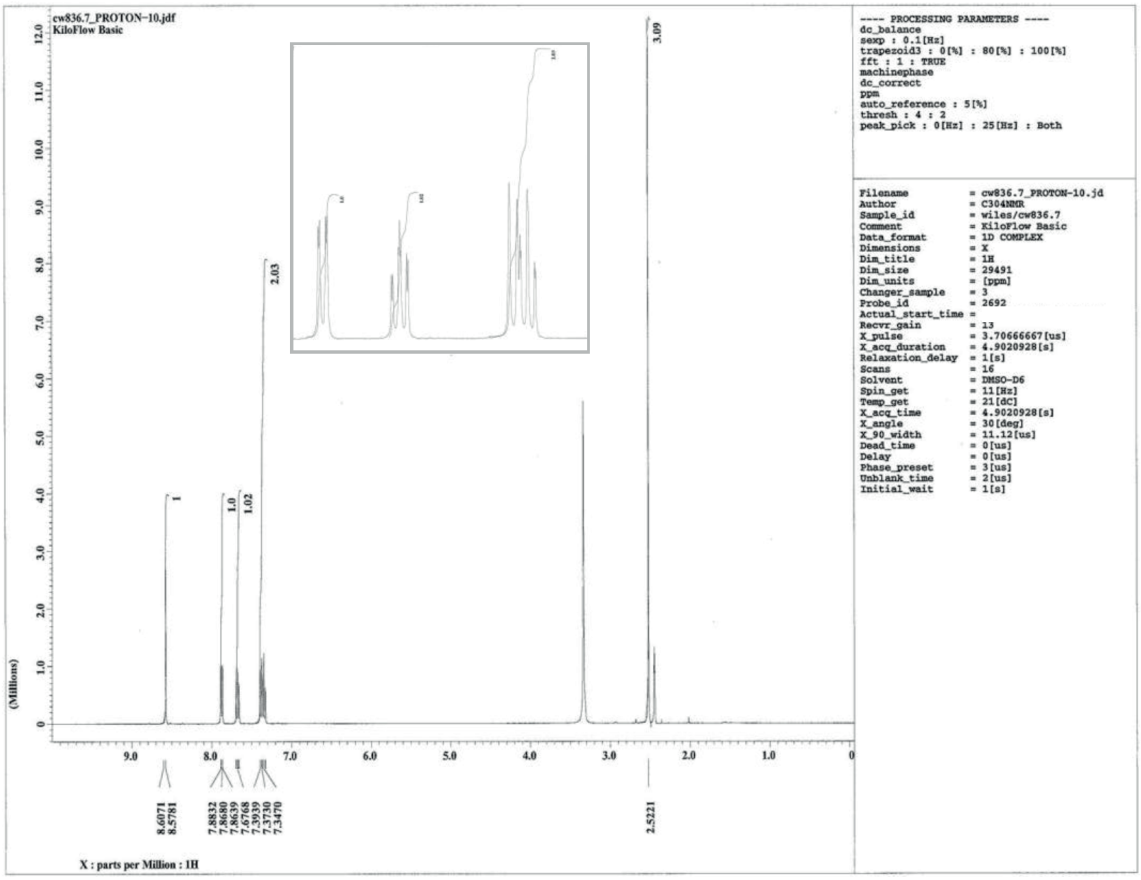


Figure 8. Illustration of the ^{1}H and ^{13}C NMR spectra of the coumarin **2** product prepared using KiloFlow® Basic.

1-(2-Methyl-2H-chromen-3-yl)ethanone ***2***: ^{1}H NMR (400 MHz, *d*-DMSO) δ 2.52 (3H, s, CH_3), 7.33-7.37 (1H, ddd, J 1.0, 1.4 and 7.3, CH), 7.39 (1H, d, J 7.3, CH), 7.65-7.70 (1H, ddd, J 1.0, 1.4 and 7.7, CH), 7.86-7.89 (1H, dd, J 1.6 and 7.7, CH) and 8.59 (1H, s, CH); ^{13}H NMR (100 MHz, *d*-DMSO) δ 30.1 (CH_3), 116.1 (CH), 118.1 (C_0), 124.4 (C_0), 124.9 (CH), 130.8 (CH), 134.5 (CH), 147.1 (CH), 154.6 (C_0), 158.4 (CO) and 195.1 ($COCH_3$); *m/z* (EI) 189 (M^++1, 4 %), 188 (50), 174 (11), 173 (100), 145 (13), 118 (13), 101 (9), 90 (7), 89 (23), 63 (12) and 43 (12).

Conclusion: We have demonstrated for the first time the 13,000x scaling of a reaction from Labtrix® to KiloFlow® Basic enabling production rates in the laboratory to be increased from 5.6 mg h^{-1} (1 µl Reactor Volume) to 73.3 g h^{-1} (13 ml Reactor Volume) without parameter re-optimisation. Employing a 60 s residence time, 0.4 eq. of base **5** and a reactor temperature of 125 ºC, 370 g of 1-(2-methyl-2*H*-chromen-3-yl) ethanone **2** was synthesised in 98 % yield in a little over 5 h; with increased production volumes readily accessible by operating KiloFlow® Basic for longer.

Note: It was not possible to perform the reaction under these conditions in EtOH as this led to product crystallisation within the system upon rapid cooling of the reaction product in the water-cooled heat exchanger ahead of the BPR.

References:

1. M. Paramjeet K., S. Dipak and D. Arti, *J. Chem. Pham. Res.*, 2012, **4**, 822-850.
2. C. Fulchand, M. Balaji, B. Jagdish, U. Milind, W. Madhav, S. Murlidhar and S. Naryn, *Bull. Catal. Soc. Ind.*, 2008, **7**, 41-45.
3. M. Maeda, *Laser Dyes*, Academic Press, New York, 1994.
4. S. C. Rastogi, J. P. Lepoittevin, J. D. Johansen, P. J. Frosch, T. Menné, M. Bruze, B. Dreier, K. E. Andersen and I. R. White, *Contact Dermatitis*, 1998, **39**(6), 293-303.
5. A.-Y. Guan, C.-L. Liu, M. Li, H. Zhang, Z.-N. Li and Z.-M. Li, *Pest Management Sci.*, 2011, **67**, 647-655.
6. F. H. Osman, N. M. A. El-Rahman, F. A. El-Samahy and I. S. A. Farag, *Phosphorus, Sulfur and Silicon and the Related Elements*, 2003, **178**, 531-538.
7. C. F. Koelsch and H. D. Embree, *J. Org. Chem.*, 1958, **23**, 1606-1608.
8. C.-Z. Tao, W.-W. Liu, J.-Y. Sun, Z.-L. Cao, H. Li and Y.-F. Zhang, *Synthesis*, 2010, **8**, 1280-1284.
9. See Application Note 15: The Scale-up of (Z)-Ethyl-2-cyano-3-phenylacrylate Synthesis; www.chemtrix.com