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Green Chemistry – Aspects for the Knoevenagel Reaction

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1. Introduction

Knoevenagel condensation is a classic C-C bond formation reaction in organic chemistry (Laue & Plagens, 2005). These condensations occur between aldehydes or ketones and active methylene compounds with ammonia or another amine as a catalyst in organic solvents (Knoevenagel, 1894). The Knoevenagel reaction is considered to be a modification of the aldol reaction; the main difference between these approaches is the higher acidity of the active methylene hydrogen when compared to an α -carbonyl hydrogen (Smith & March, 2001).

Figure 1 illustrates the condensation of a ketone (1) with a malonate compound (2) to form the Knoevenagel condensation product (3), which is then used to form the α,β -unsaturated carboxylic compounds (3) and (4) (Laue & Plagens, 2005).

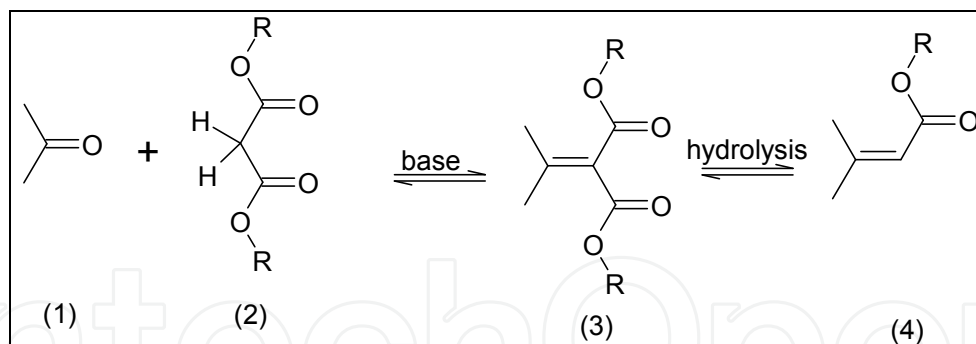


Fig. 1. An example of the Knoevenagel reaction.

Subsequent to the first description of the Knoevenagel reaction, changes were introduced using pyridine as the solvent and piperidine as the catalyst, which was named the Doebner Modification (Doebner, 1900). The Henry reaction is another variation of the Knoevenagel condensation that utilises compounds with an α -nitro active methylene (Henry, 1895). The general mechanism for the Knoevenagel reaction, which involves deprotonation of the malonate derivative (6) by piperidine (5) and attack by the formed carbanion (8) on the carbonyl subunit (9) as an aldol reaction that forms the product (10) of the addition step is illustrated in Fig. 2. After the proton transfer step between the protonated base (7) and compound (10), intermediate (11) forms and is then deprotonated to (12), which forms the elimination product (13) in the last step.

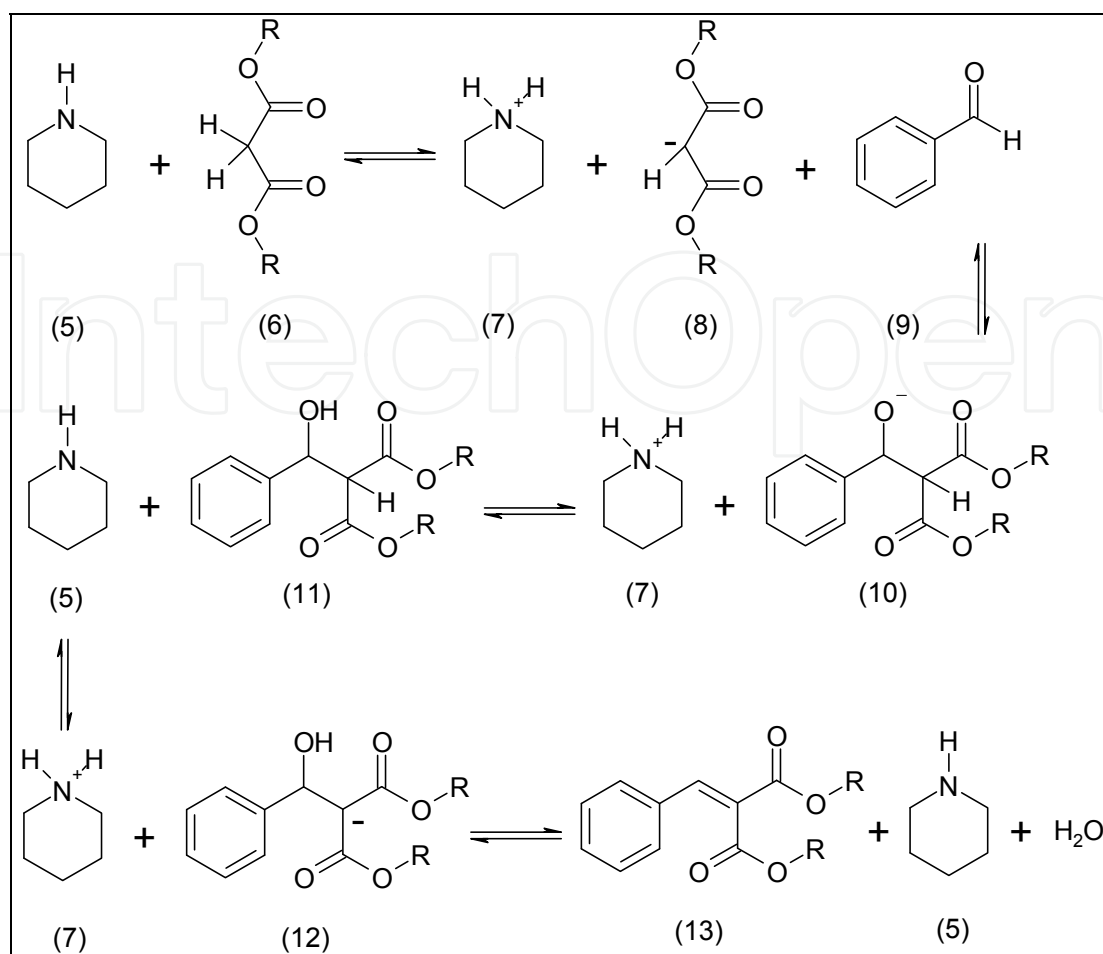


Fig. 2. General mechanism for the Knoevenagel reaction.

2. Green chemistry and new synthetic approaches

In the past two decades, classic organic chemistry had been rewritten around new approaches that search for products and processes in the chemical industry that are environmentally acceptable (Okkerse & Bekkum, 1999; Sheldon et al., 2007). With the emergence of Green Chemistry, a term coined in 1993 by Anastas at the US Environmental Protection Agency (EPA), a set of principles was proposed for the development of environmentally safer products and processes: waste prevention instead of remediation; atom efficiency; less hazardous/toxic chemicals; safer products by design; innocuous solvents and auxiliaries; energy efficiency by design; preference for renewable raw materials; shorter syntheses; catalytic rather than stoichiometric reagents; products designed for degradation; analytical methodologies for pollution prevention; and inherently safer processes (Anastas & Warner, 2000).

Consequently, many classic reactions, such as the Knoevenagel reaction, have been studied based upon the green chemistry perspective, which is very important in the context of the pharmaceutical industry. Currently, two indicators are used to evaluate environmental acceptability of products and chemical processes. The first is the Environmental factor (E factor), which measures the mass ratio of kg of waste to kg of desired product, as described by Sheldon in 1992 (Sheldon, 2007). The second indicator is a measure of atom economy

based on the ratio of the molecular weight of the desired product to the sum of the molecular weights of all stoichiometric reagents. This indicator enables the evaluation of atom utilisation in a reaction (Trost, 1991). As illustrated in Table 1, the pharmaceutical industry produces 25->100 kg of waste per kg of drug produced, which is the worst E factor observed among the surveyed industrial sectors (Sheldon, 2007). This result is problematic as the pharmaceutical market is among the major sectors of the global economy, accounting for US \$ 856 billion in 2010 (Gatyas, 2011a).

Industrial sector	Annual product tonnage	kg waste/kg product
Oil refining	10 ⁶ -10 ⁸	ca. 0.1
Bulk chemicals	10 ⁴ -10 ⁶	<1-5
Fine chemicals	10 ² -10 ⁴	5->50
Pharmaceuticals	10-10 ³	25->100

Table 1. The E Factor for selected industrial sectors, left justified.

Among the 20 top-selling drugs of 2010, atorvastatin (14) is at the top of the list, corresponding to US \$ 12.6 billion in sales (Gatyas, 2011b). One step in the synthesis of atorvastatin (14) (Fig. 3) uses a Knoevenagel condensation between methylene compound (15) and benzaldehyde (9) to produce an intermediate (16) in yields of 85.0% (Li et al., 2004; Roth, 1993).

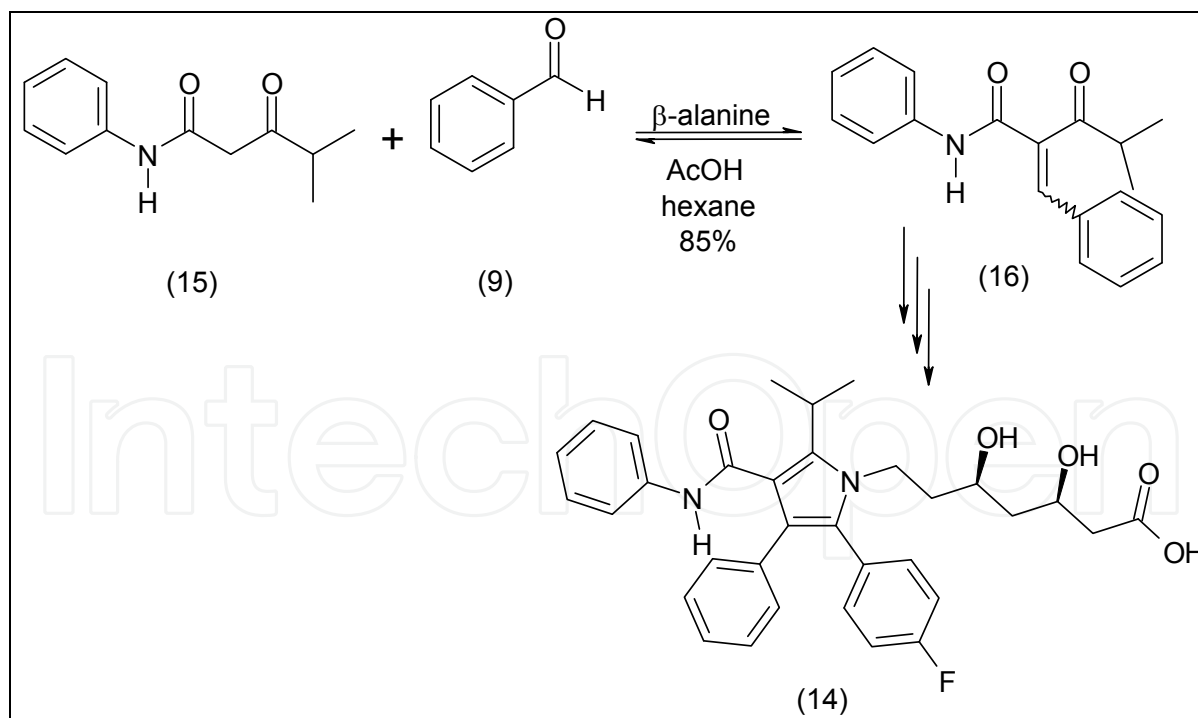


Fig. 3. A Knoevenagel condensation used during the synthesis of atorvastatin (14).

In addition to atorvastatin (14), many others drugs and pharmacological tools use the Knoevenagel reaction during their syntheses. Figure 4 illustrates the synthesis of pioglitazone (17), a benzylthiazolidinedione derivative approved as a drug for the

management of diabetes (Madivada et al., 2009). In this synthesis, the key intermediate (20) was formed in yields of 94.5% through the piperidine-catalysed reaction of aldehyde intermediate (18) and 2,4-thiozolidinedione (19) (Madivada et al., 2009).

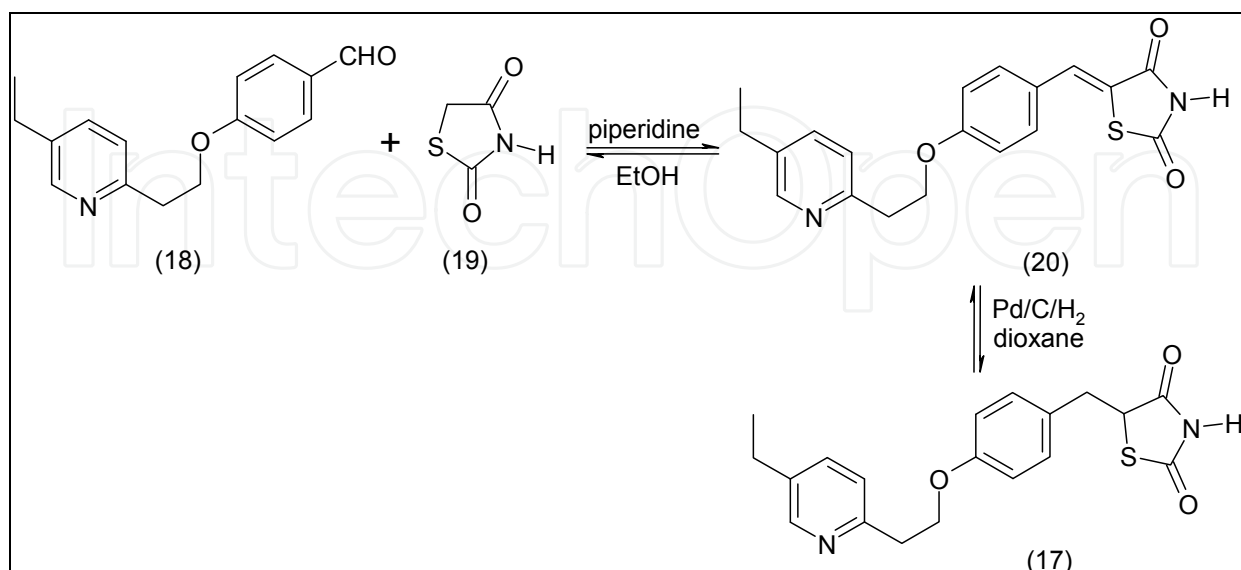


Fig. 4. Selected steps of the pioglitazone (17) synthesis.

AMG 837 (21) is a novel agonist of GPR40; this compound is being investigated as a potentially new therapeutic agent for the treatment of type 2 diabetes (Walker et al., 2011). As shown in Fig. 5, the synthetic route for AMG 837 (21) involves the production of intermediate (24), which is formed in yields of 97.0% via the reaction between aldehyde (22) with Meldrum's acid (23), using water/toluene (10/1) as a catalytic solvent (Walker et al., 2011).

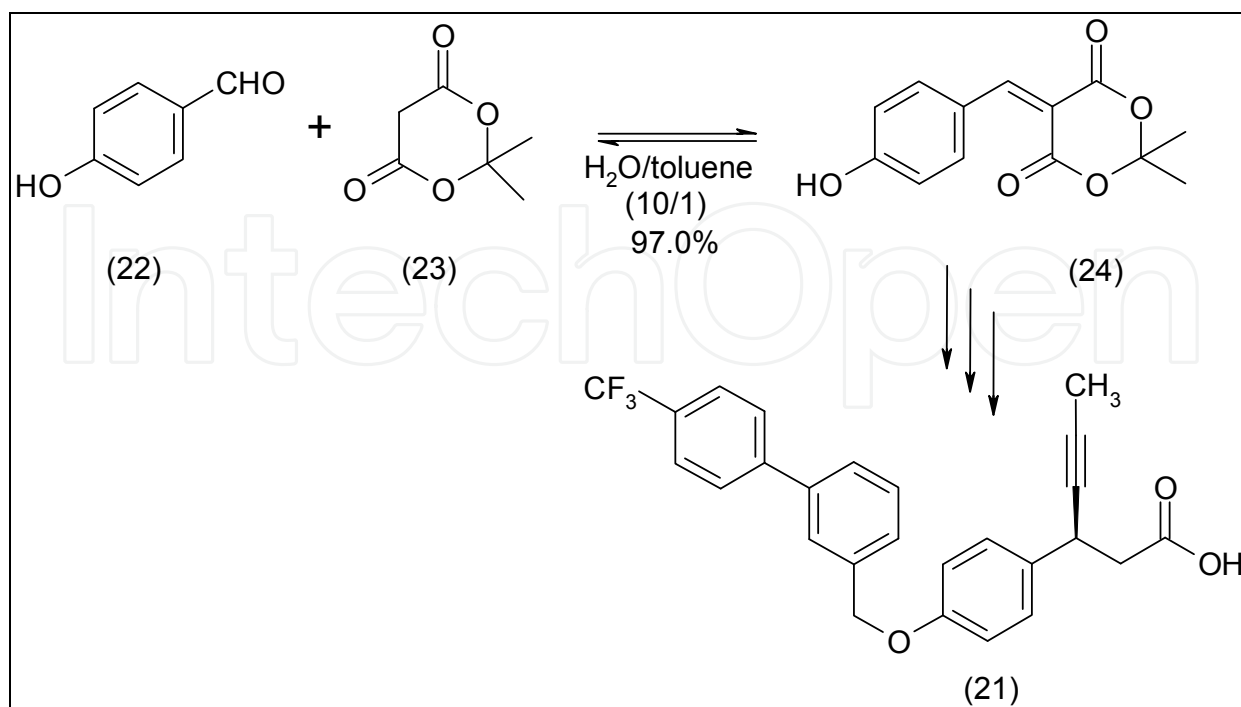


Fig. 5. AMG 837 (21) synthesis.

MDL 103371 (25) is an *N*-methyl-*D*-aspartate-type glycine receptor antagonist for the treatment of stroke (Watson et al., 2000). As illustrated in Fig. 6, synthesis of MDL 103371 (25) involves production of key intermediate (28) in yields of 91.0% via the condensation of 4,6-dichloro-3-formyl-1*H*-indole-2-carboxylate (26) with 3-nitrophenylacetonitrile (27); this piperidine-catalysed step is carried out using ethanol under reflux conditions for 70 hours (Walker et al., 2011).

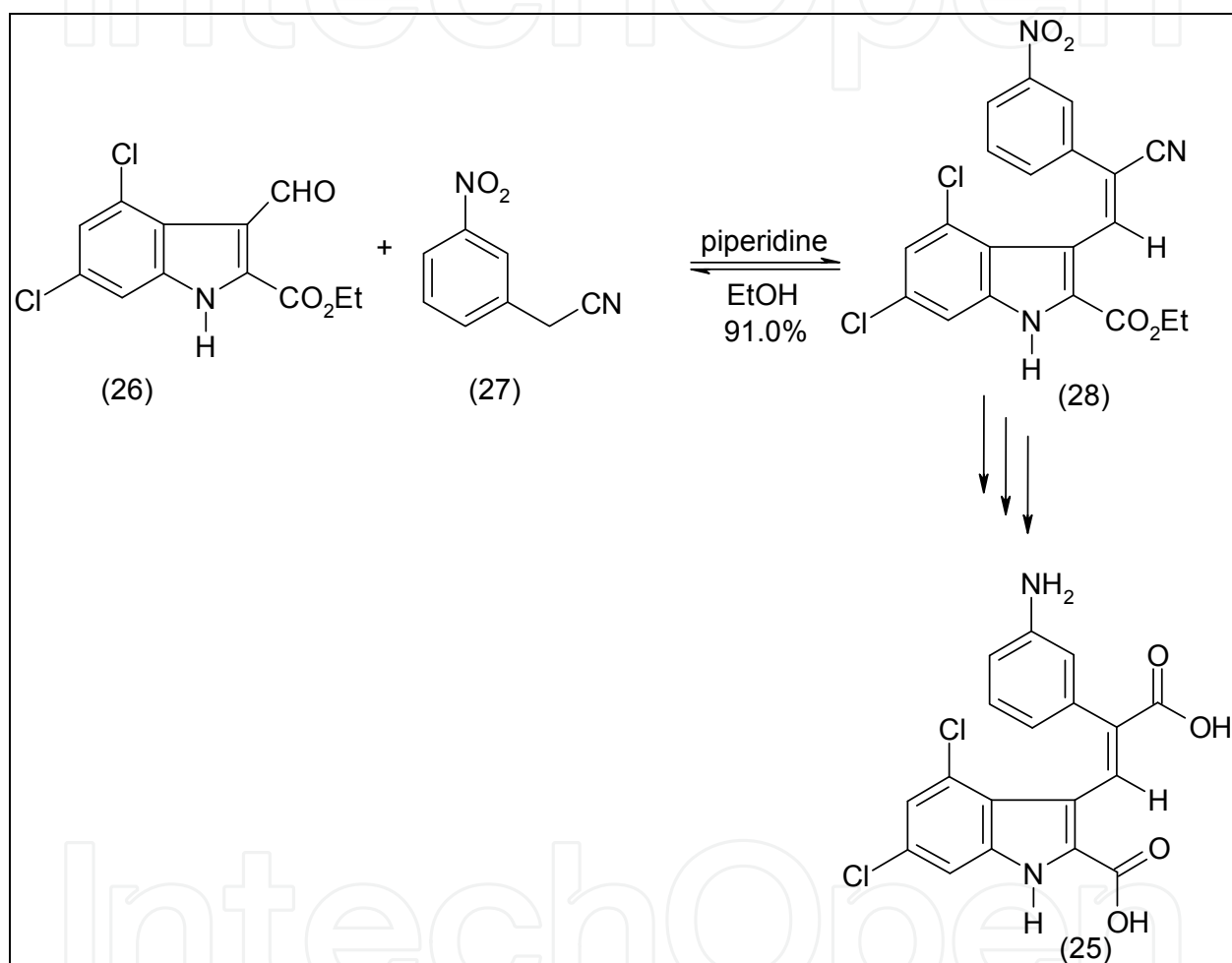


Fig. 6. MDL 103371 (25) synthesis.

(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid, or pregabalin (29), is a lipophilic GABA (γ -aminobutyric acid) analogue used for the treatment of several central nervous system (CNS) disorders, such as epilepsy, neuropathic pain, anxiety and social phobia (Martinez et al., 2008). As shown in Fig. 7, intermediate (32), which is produced during the synthesis of pregabalin (29), is formed in yields of 95.0% from the reaction between isovaleraldehyde (30) and diethyl malonate (31) using acetic acid as the solvent and di-*n*-propylamine as the catalyst.

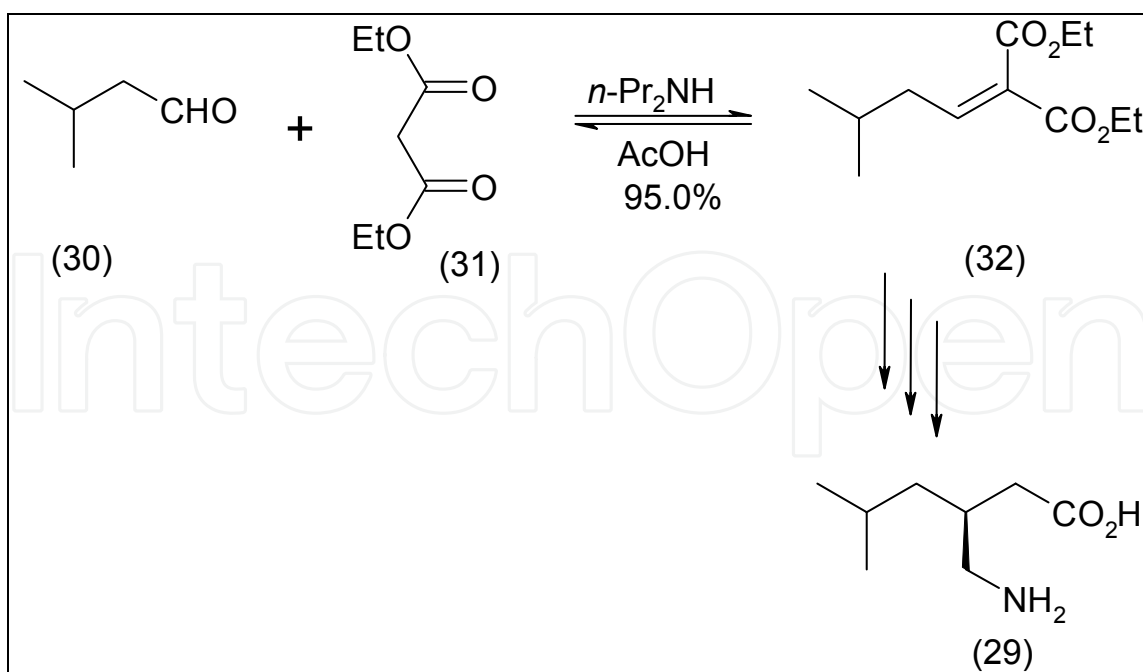


Fig. 7. Pregabalin (29) synthesis.

(*E*)-4-Cyclobutyl-2-[2-(3-nitrophenyl)ethenyl] thiazole, or Ro 24-5913 (33), is a leukotriene antagonist that has been utilised as a pharmacological tool to study asthma as well as other inflammatory diseases (Kuzemko et al., 2007). One method used to prepare Ro 24-5913 (33), illustrated in Fig. 8, is under Doebner conditions in which 3-nitrobenzaldehyde (34) reacts in the first step with malonic acid to produce intermediate (36) in yields of 65.6% (Kuzemko et al., 2007).

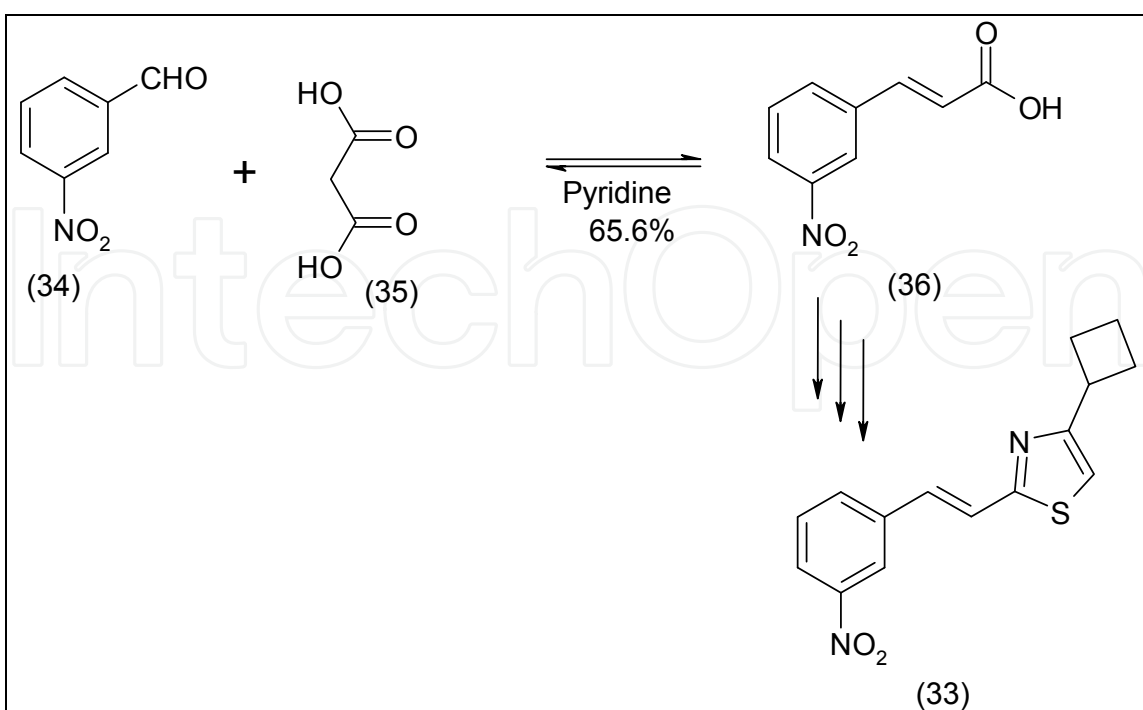


Fig. 8. Ro 24-5913 (33) synthesis.

Coartem is an antimalarial drug that is a combination of artemether and lumefantrine (37) (Beulter et al., 2007). This combination greatly benefits patients because it facilitates treatment compliance and supports optimal clinical effectiveness. As shown in Fig. 9, crude lumefantrine (37) was produced in yields of 88.0% via the reaction of 4-chlorobenzaldehyde (39) with methylene compound (38) in ethanol with sodium hydroxide as a catalyst. After crystallisation in heptane, pure lumefantrine (37) was generated in yields of 93.0% (Beulter et al., 2007).

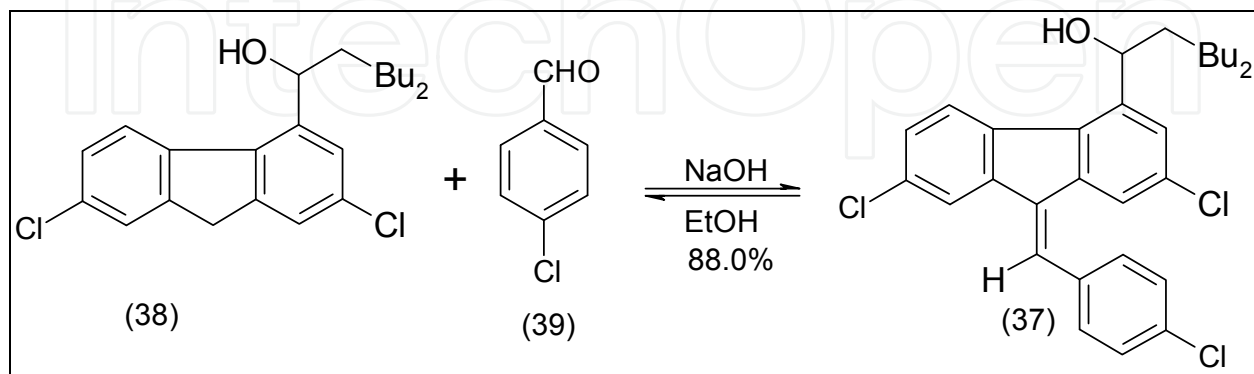


Fig. 9. Lumefantrine (37) synthesis.

Entacapone (40) is a catechol-O-methyltransferase (COMT) inhibitor used in combination with *L*-DOPA for the treatment of Parkinson's disease (Mukarram et al., 2007). This combination prevents *L*-DOPA degradation through COMT inhibition. As illustrated in Fig. 10, this drug (40) is synthesised in yields of 73.0% from aldehyde (41) and methylene compound (42) in ethanol with a piperidine catalyst (Mukarram et al., 2007).

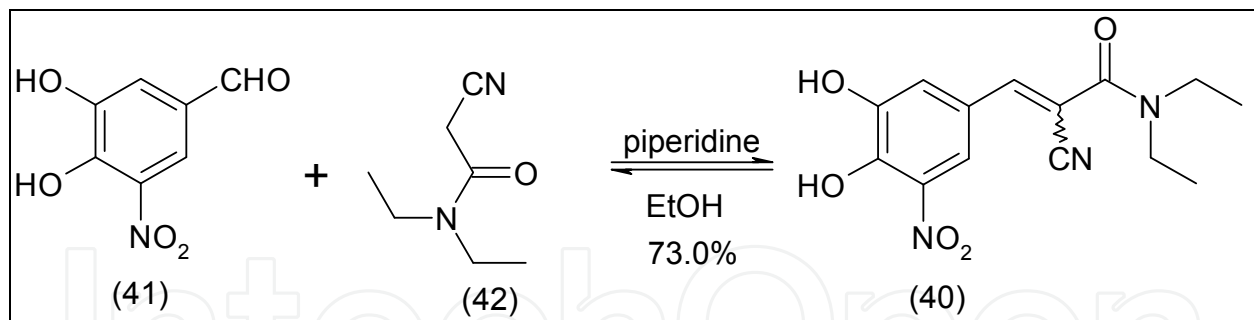


Fig. 10. Entacapone (40) synthesis.

The examples illustrated above for selected drug syntheses emphasise the on-going necessity of finding new approaches to carry out classic reactions that are essential to developing environmentally responsible products and chemical processes. Some new, green approaches are presented below.

2.1 Microwave-promoted Knoevenagel reactions

Microwave irradiation is a method used to speed up reactions with potential uses under the guidelines of Green Chemistry principles. Microwave radiation utilises wavelengths of 0.001 – 1 m and frequencies of 0.3 – 300 GHz. When a polar organic reaction is irradiated in a microwave, energy is transferred to the sample, and the result is an increase in the rate of

reaction. The transference of energy from microwave radiation to the sample is accomplished through dipolar polarisation and conduction mechanisms (Lidström et al. 2001; Loupy, 2002). As illustrated in Fig. 11, the coumarinic derivative (42) is produced in yields of 75.0% after eight minutes of irradiation. This reaction was carried out using aldehyde (43) and methylene compound (44) and was catalysed by piperidine without solvent present (Bogdal, 1998). Following the Knoevenagel condensation, the transesterification reaction to form the ring quickly occurs.

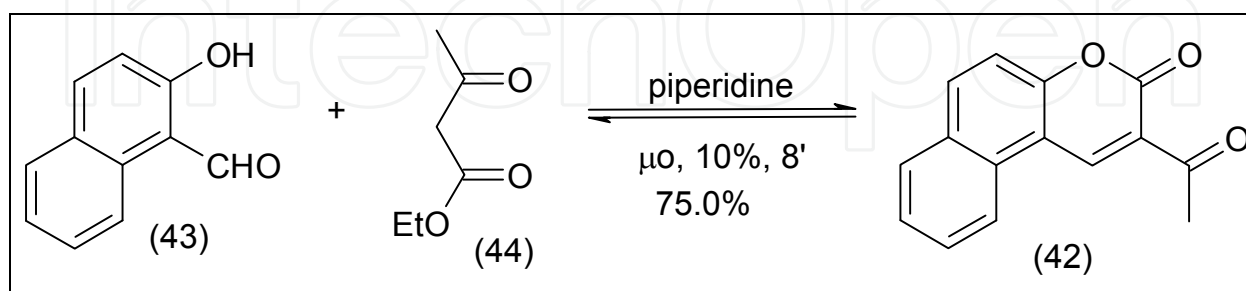


Fig. 11. Coumarinic derivative (42) synthesis.

There are many examples in the literature involving the use of microwave radiation to promote Knoevenagel reactions. In these examples, several different aldehydes, methylene compounds and catalysts were used for the syntheses involving cinnamic acids on silica gel (Kumar et al., 2000), ammonium acetate (Kumar et al., 1998; Mitra et al., 1999) and lithium chloride as catalysts (Mogilaiah & Reddy, 2004).

2.2 Clays as catalysts for Knoevenagel reactions

Clays are abundant in nature, and their high surface area, utility as supports and ion-exchange properties have been exploited for catalytic applications (Dasgupta & Török, 2008; Varma, 2002). As shown in Fig. 12, the product of Knoevenagel reaction (45) from the reaction between ninhydrin (46) and malononitrile (47) can be formed in yields of 85.0% after five minutes. This reaction was carried out at room temperature without solvent using K10 as a catalyst (Chakrabarty et al., 2009).

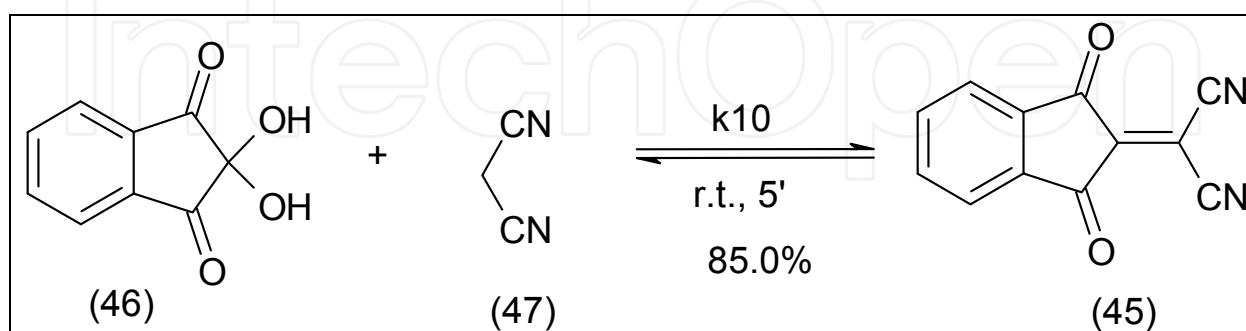


Fig. 12. Knoevenagel product (45) synthesis.

Other Knoevenagel reactions between aromatic aldehydes and malononitrile (47) have also performed successfully without solvent using calcite or fluorite catalysts prepared using a ball mill (Wada & Suzuki, 2003).

2.3 The use of ionic liquids in Knoevenagel reactions

In recent years, ionic liquids (ILs) have attracted increasing interest as environmentally benign solvents and catalysts due to their relatively low viscosities, low vapour pressures and high thermal and chemical stabilities (Hajipour & Rafiee, 2010; Wasserscheid & Welton, 2002). ILs have been successfully used in a variety of reactions.

As illustrated in Fig 13, the pyrazolonic compound (48) was produced in yields of 71.0% from the reaction between benzaldehyde (9) and 3-methyl-1-phenylpyrazolin-5-(4*H*)-one (49) after 30 minutes using ethylammonium nitrate as an ionic liquid at room temperature (Hangarge et al., 2002).

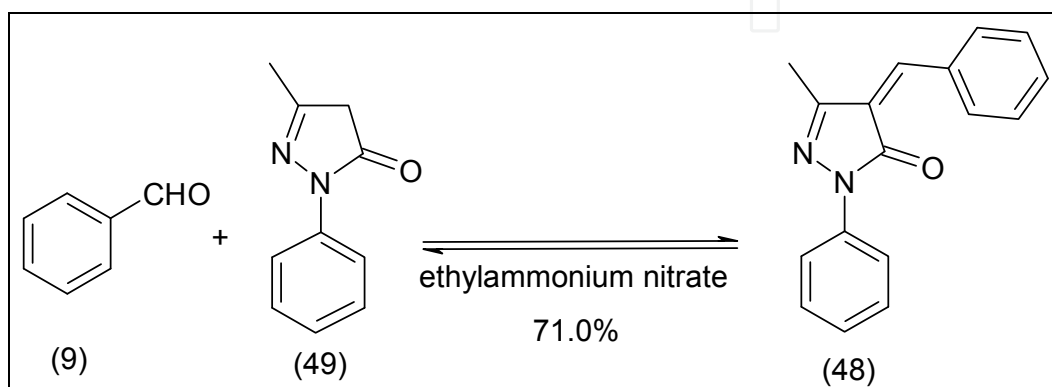


Fig. 13. Compound (48) synthesis.

Other reactions between aromatic aldehydes and methylene compounds that were catalysed by 1,3-dimethylimidazolium methyl sulphate [MMIm][MSO₄] and 2.16% water have been carried out in good yields (Verdía et al., 2011),

2.4 Catalysis of Knoevenagel reactions using biotechnology

Historically, microorganisms have been of enormous social and economic importance (Liese et al., 2006). In the pharmaceutical industry, companies are using biotechnology to develop 901 medicines and vaccines targeting more than 100 diseases (Castellani, 2001a). In 2010, 26 new treatments were approved, and five of these treatments were based on biotechnology (Castellani, 2001b).

Using a biotechnology-based approach, coumarin (50) was produced in yields of 58.0% when the reaction was catalysed by alkaline protease from *Bacillus licheniformis* (BLAP) in a DMSO:H₂O (9:1) solvent at a temperature of 55°C (Fig. 14) (Wang et al., 2011).

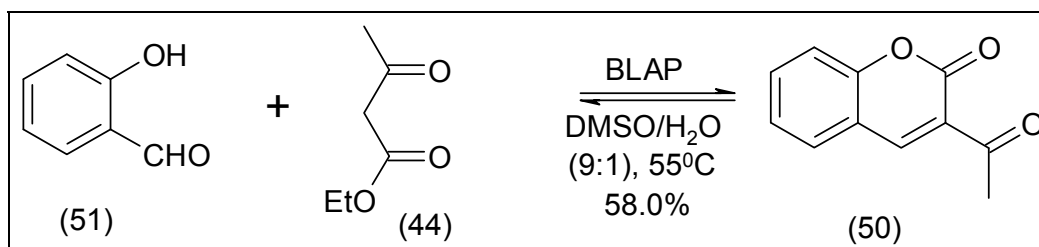


Fig. 14. Coumarin (50) synthesis using BLAP.

Because cells are chemical systems that must conform to all chemical and physical laws, whole microorganisms may be used (Alberts et al., 2002). Figure 15 illustrates examples of other Knoevenagel products (52) and (53) resulting from reactions between benzaldehyde (9) and methylene compounds (44) and (19) that were catalysed by baker's yeast. These reactions were carried out under mild conditions, e.g., room temperature and in ethanol as the solvent, with moderate to good yields (Pratap et al., 2011).

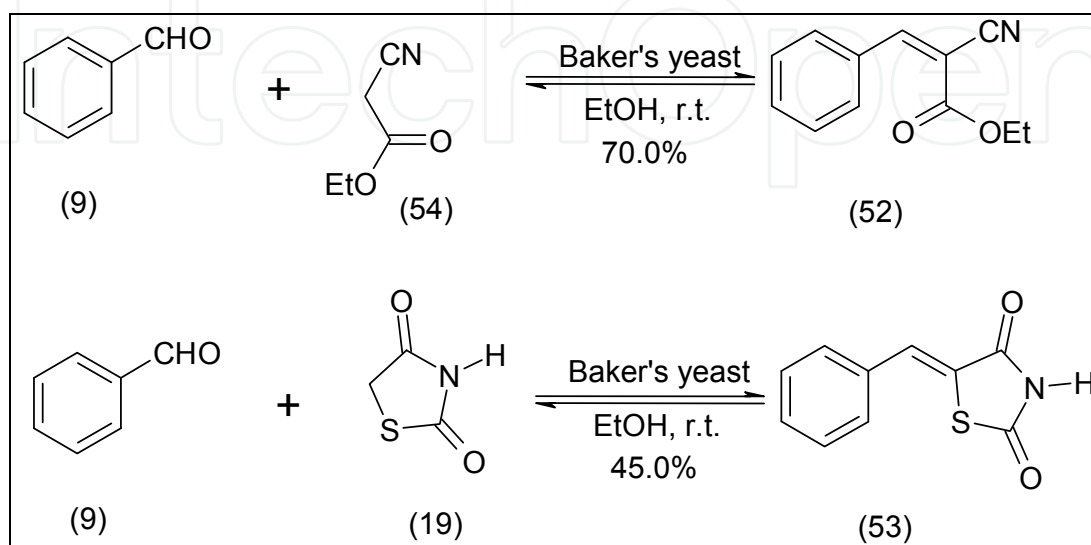


Fig. 15. Knoevenagel reactions using a biotechnology-based approach.

2.5 Knoevenagel reactions in water

Water as a solvent is not only inexpensive and environmentally benign but also provides completely different reactivity (Li & Chen, 2006). It has been suggested that the effect of water on organic reactions may be due to the high internal pressure exerted by a water solution, which results from the high cohesive energy of water (Breslow, 1991).

As illustrated in Fig. 16, the Knoevenagel reaction product (55) is formed in yields of 97.0% when condensation between aldehyde (56) and malononitrile (47) was carried out in water at a temperature of 65°C in the absence of catalyst (Bigi et al., 2000).

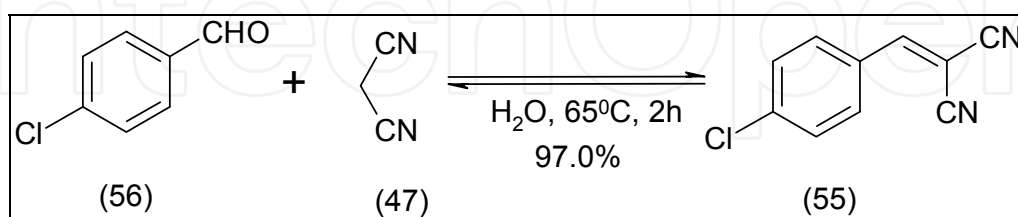


Fig. 16. A Knoevenagel reaction carried out in water.

The product of the reaction between vanillin (58) and ethyl cyanoacetate (54) was formed in yields of 84.5% in water at room temperature (Fig. 17) (Gomes et al., 2011). This compound was patented in 2007 by Merck & Co. for use in sunscreen compositions containing a UVA sunscreen, photostabiliser and antioxidant. The reaction was carried out using piperidine as the catalyst and acetic acid/benzene as the solvent under reflux conditions for

approximately 90 minutes, producing yields of 95.0% (Ratan, 2007). Thus, it's clear that there are green approaches for carrying out organic reactions in water to prepare compounds of industrial interest.

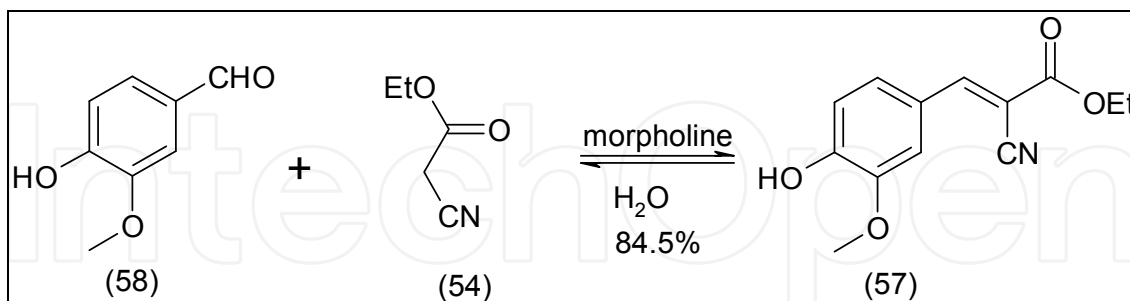


Fig. 17. Morphonile-catalysed synthesis of sunscreen in water.

Entacapone (40), a COMT inhibitor drug whose synthesis is illustrated above in Fig. 10, is another example of the synthesis of important industrial compounds using green conditions. As shown in Fig. 18, Knoevenagel reaction product (59) is formed in yields of 88.0% after two hours under reflux in water with piperidine as a catalyst (McCluskey, 2002).

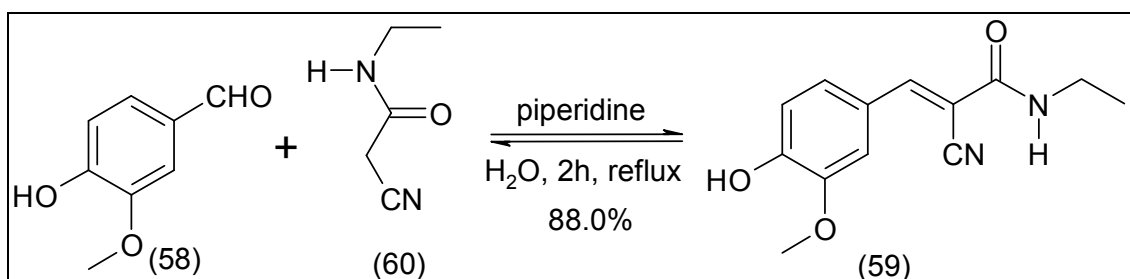


Fig. 18. Compound (59) synthesis.

There are others examples of Knoevenagel reactions carried out in water that are catalysed by *L*-histidine and *L*-arginine (Rhamati & Vakili, 2010). Isatin compounds (61) can also be produced in water at room temperature after fifteen minutes in yields of 75.0% (Fig. 19) (Demchuk, 2011).

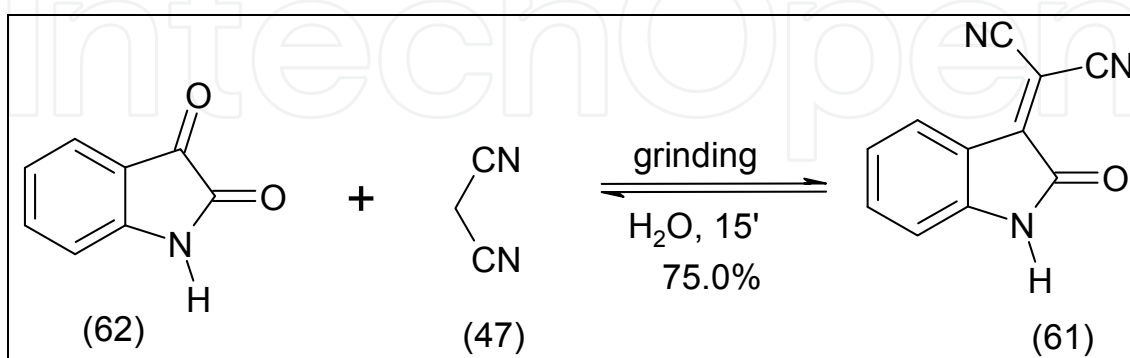


Fig. 19. Isatin compound (61) synthesis.

Knoevenagel reactions can also be used to assemble a benzo[*b*]pyrane [4,3-*d*][1,2]oxazine-2-oxide skeleton (63) and (64) via a domino-effect Knoevenagel–Diels–Alder process (Fig. 20)

(Amantini, 2001). When the prenylated phenolic aldehyde (65) reacts with methylene compound (66) in water at room temperature for three hours, Knoevenagel intermediate (67) forms, which then reacts to form Diels-Alder product (63) and (64) in yields of 75.0% at a 16:1 ratio (Amantini, 2001).

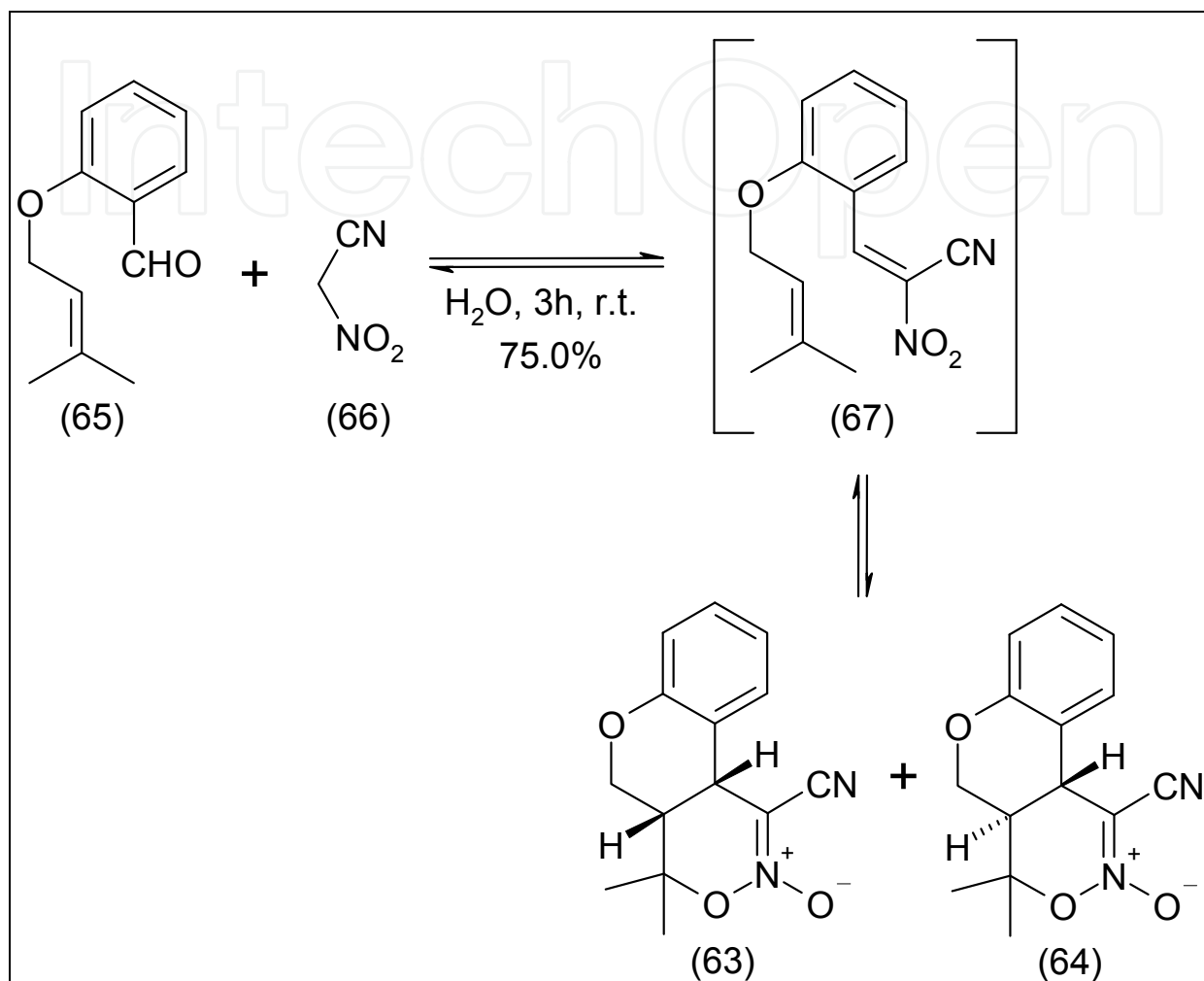


Fig. 20. Synthesis of benzo[*b*]pyrane [4,3-*d*][1,2]oxazine-2-oxide skeletons (63) and (64).

2.6 Ultrasound-catalysed Knoevenagel reactions

The application of ultrasound waves triggers high-energy chemistry, which is thought to occur through the process of acoustic cavitation, i.e., the formation, growth and implosive collapse of bubbles in a liquid. During cavitation collapse, intense heating of the bubbles occurs (Suslick, 1990).

The piperidine-catalysed reaction between piperonal (69) and malonic acid (35) at room temperature with pyridine as the solvent was carried out under ultrasound irradiation, and Knoevenagel reaction product (68) formed in yields of 91.0% after three hours (Fig. 21) (McNulty et al., 1998). When carried out under reflux conditions, the same reaction forms the Knoevenagel reaction product in yields of 52.0% after three hours (McNulty et al., 1998).

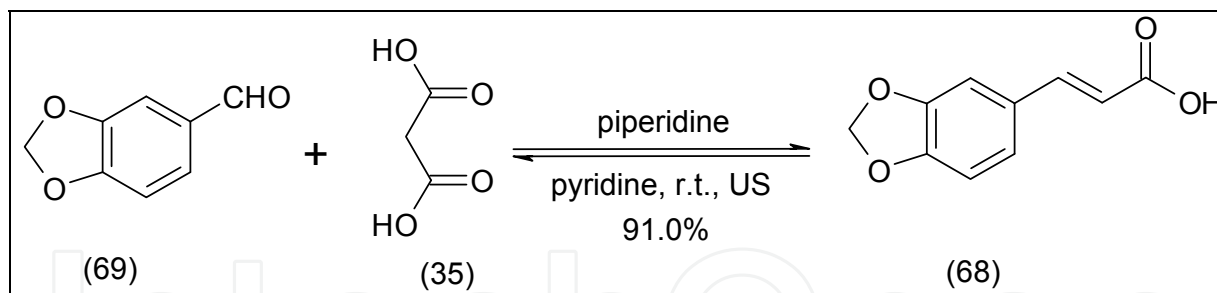


Fig. 21. Ultrasound-catalysed synthesis of Knoevenagel reaction product (68).

Figure 22 illustrates reactions between benzaldehyde (9) and coumarin (71) that can also be conducted in water under ultrasound irradiation at a temperature of 40°C for 90 minutes, forming product (70) in yields of 88.0% (Method B) (Palmisano et al., 2011). In the absence of ultrasound irradiation, formation of product (70) occurs in yields of 62.0% under anhydric conditions (Method A) (Palmisano et al., 2011).

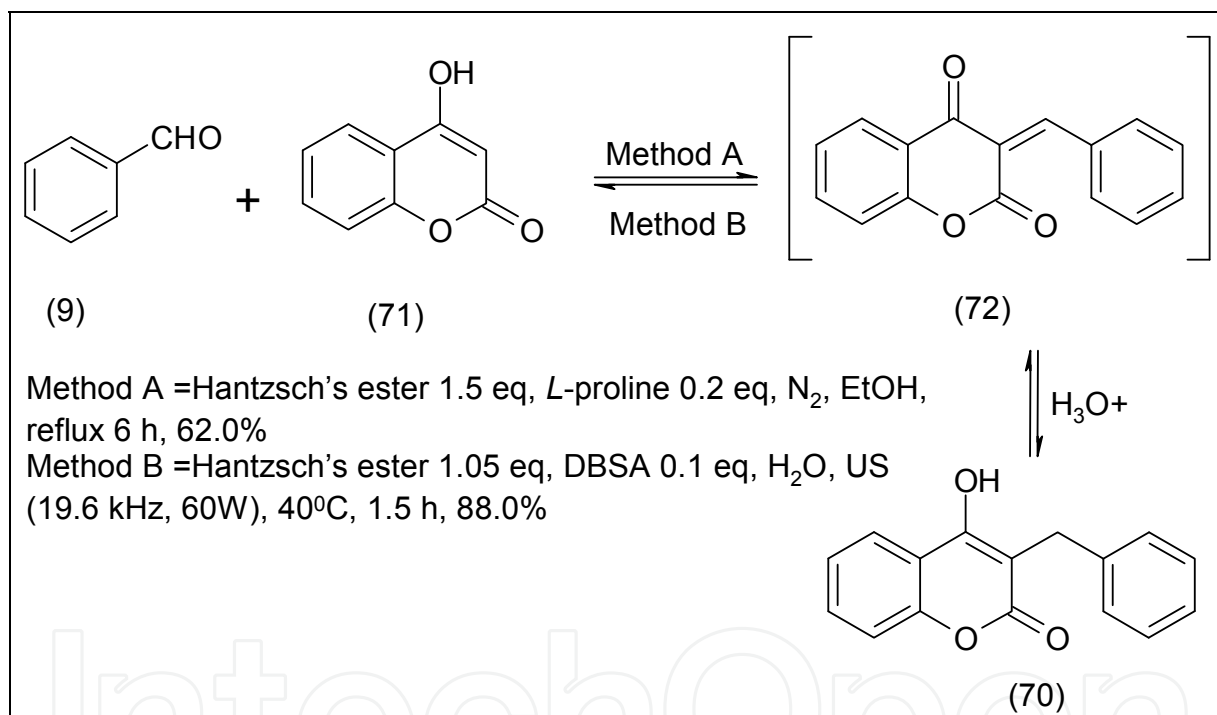


Fig. 22. Synthesis of coumarinic compound (70) with and without ultrasound irradiation.

2.7 Solvent-free Knoevenagel reactions

As mentioned previously, the reduction or elimination of volatile organic solvents in organic syntheses is one of the main goals in green chemistry. Solvent-free organic reactions result in syntheses that are simpler and less energy-intensive, and these conditions also reduce or eliminate solvent waste, hazards, and toxicity (Tanaka, 2003).

One method of solvent-free organic synthesis uses high pressure, as shown in Fig. 22 (Jenner, 2001). The piperidine-catalysed reaction between 2-butanone (75) and ethyl cyanoacetate (54) was carried out using two methods in which formation of E(73)/Z(74) Knoevenagel reaction products was observed. When the pressure was increased from 0.10

MPa to 300 MPa, the yield increased from 28.1% to 99.0%. However, significant changes were not observed in the ratio of E(73)/Z(74) Knoevenagel reaction products (Jenner, 2001).

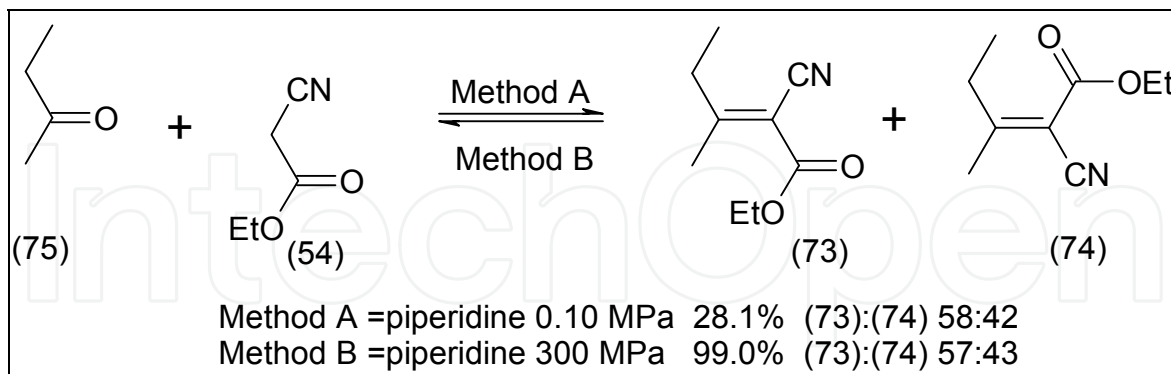


Fig. 23. High-pressure Knoevenagel reactions.

Solvent-free Knoevenagel reactions have also been carried out using a mortar and pestle. Under these conditions, the reaction between benzaldehyde (9) diethyl malonate (31), which was catalysed by triethylbenzylammonium chloride (TEBA), resulted in product yields of 87.5% after ten minutes (Rong et al., 2006). Similarly, the domino-effect Friedlander condensation reaction, which can also be conducted using a mortar and pestle, was observed between aldehyde (77) and methylene compound (78). This sodium fluoride-catalysed reaction formed the aromatic Knoevenagel reaction product (76) in yields of 92.0% after eight minutes (Fig. 24) (Mogilaiah & Reddy, 2003).

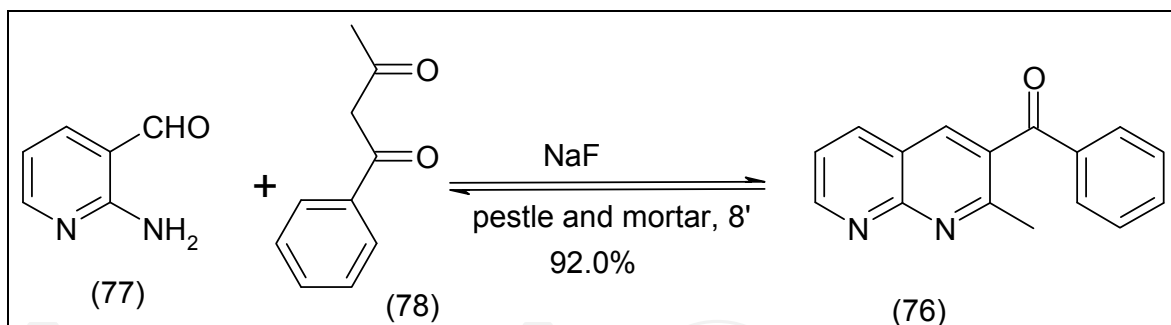


Fig. 24. Synthesis of the Friedlander condensation product (76).

2.8 Knoevenagel reactions using solid phase organic synthesis

An innovative and important field of organic synthesis involves the use of solid phase organic synthesis (Czarnik, 2001). This new methodology was introduced by Merrifield in 1963 when he used it to synthesise amino acids (Merrifield, 1963). Solid phase organic synthesis uses insoluble polymers that covalently bond organic substrates to the solid surface until the synthesis is complete, at which point the compound of interest is separated from the solid matrix (Czarnik, 2001).

This approach has been used to synthesise coumaric compound (79) from the reaction of aldehyde (81) and methylene compound (80) bonded to Wang resin. The reaction was complete after sixteen hours under Doebner conditions, as illustrated in Fig. 25 (Xia et al., 1999).

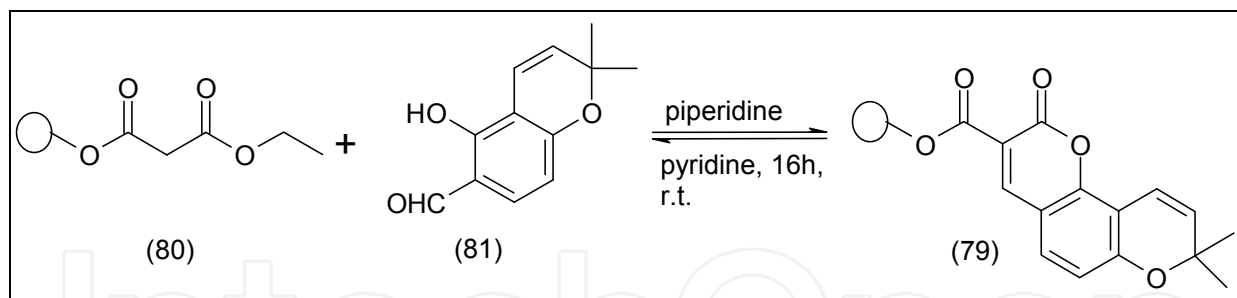


Fig. 25. Synthesis of coumarin (79) via solid phase organic synthesis.

Solid phase Knoevenagel reactions were also utilised to produce triphostin protein tyrosine kinases inhibitors. As illustrated in Fig. 26, the piperidine-catalysed reaction between 4-hydroxybenzaldehyde (22) and a resin-bonded methylene compound (83) was carried out using DMF:MeOH (10:1) as the solvent over a period of twelve hours (Guo et al., 1999).

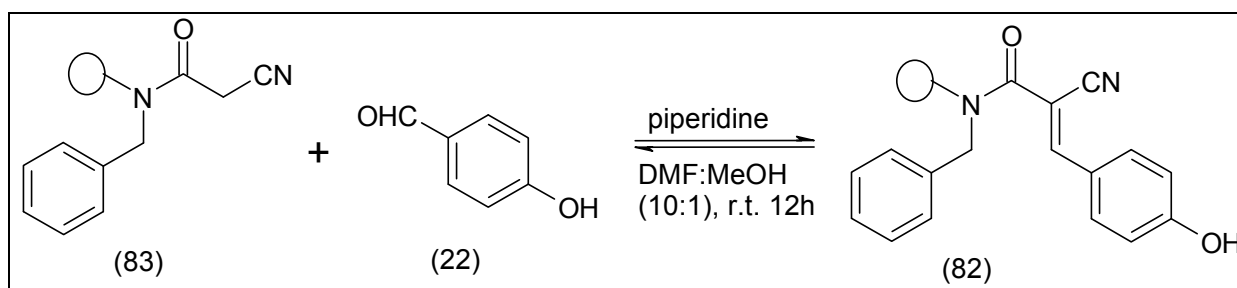


Fig. 26. Synthesis of triphostin (82) via solid phase organic synthesis.

3. Conclusions

As illustrated by the examples presented herein, classic reactions such as the Knoevenagel condensation can be modernised through new approaches related to Green Chemistry. Particularly in the area of drug synthesis, these new approaches have been being very useful in the development of more environmentally supportable products and chemical processes in the pharmaceutical industry, which works with compounds with high added values.

4. Acknowledgments

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5. References

- Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K. & Walter, P. (2002). *Molecular Biology of The Cell*, Garland Science, ISBN 0-8153-3218-1, New York, USA
- Amantini, D., Fringuelli, F., Piermatti, O., Pizzo, F. & Vaccaro, L. (2001). Water, a clean, inexpensive, and re-usable reaction medium. One-pot synthesis of (*E*)-2-aryl-1-cyano-1-nitroethenes. *Green Chemistry*, Vol.3, No.5, (September 2001), pp. 229-232, ISSN 1463-9262

- Anastas, P. T. & Warner, J.C. (2000). *Green Chemistry : Theory and Practice*, Oxford University Press, ISBN 0-19-850698-8, New York, USA
- Beutler, U., Fuenfschilling, P. C. & Steinkemper, A. (2007). An Improved Manufacturing Process for the Antimalaria Drug Coartem. Part II. *Organic Process Research & Development*, Vol.11, No.3, (June 2007), pp. 470-476, ISSN 341-345
- Bigi, F., Conforti, M. L., Maggi, R., Piccinno, A. & Sartori, G. (2000). Clean synthesis in water: uncatalysed preparation of ylidenemalononitriles. *Green Chemistry*, Vol.2, No.3, (May 2000), pp. 101-103, ISSN 1463-9262
- Bogdal, D. (1998). Coumarins: Fast Synthesis by Knoevenagel Condensation under Microwave Irradiation. *Journal of Chemical Research (S)*, (March 1998), pp. 468-469, ISSN 1747-5198
- Breslow, R. (1991). Hydrophobic Effects on Simple Organic Reactions in Water. *Accounts of Chemical Research*, Vol.24, No.6, (June 1991), pp. 159-164, ISSN 0001-4842
- Burgess, K. (2000). *Solid-Phase Organic Synthesis*, John Wiley & Sons, Inc., ISBN 0-471-31825-6, New York, USA
- Castellani, J. J. (September 2011a). Medicines in development Biotechnology, 23.09.2011, Available from <http://www.phrma.org/sites/default/files/1776/biotech2011.pdf>
- Castellani, J. J. (September 2011b). New Drug Approvals in 2010, 23.09.2011, Available from <http://www.phrma.org/sites/default/files/422/newdrugapprovals2010.pdf>
- Chakrabarty, M., Mukherji, A., Arima, S., Harigaya, Y. & Pilet, G. (2009). Expeditious reaction of ninhydrin with active methylene compounds on montmorillonite K10 clay. *Monatshefte für Chemie*, Vol.140, No.2, (February 2009), pp. 189-197, ISSN 0026-9247
- Czarnik, A. W. (2001). *Solid-Phase Organic Syntheses*, John Wiley & Sons, Inc., ISBN 0-471-31484-6, New York, USA
- Dasgupta, S. & Török, B. (2008). Application of Clay Catalysts in Organic Synthesis. A Review. *Organic Preparations and Procedures International*, Vol.40, No.1, (February 2008), pp. 1-65, ISSN 0030-4948
- Demchuk, D. V., Elinson, M. N. & Nikishin, G. I. (2011). 'On water' Knoevenagel condensation of isatins with malononitrile. *Mendeleev Communications*, Vol.21, No.4, (July-August 2011), pp. 224-225, ISSN 0959-9436
- Doebner, O. (1900). Synthese der Sorbinsäure. *Berichte der Deutschen Chemischen Gesellschaft*, Vol.33, No.2, (Mai-August 1900), pp. 2140-2142, ISSN 0365-9631
- Gatyas, G. (August 2011a). Global Pharmaceutical Sales 2003-2010, 10.08.2011, Available from http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2010%20Top-line%20Market%20Data/Total_Market_2003-2010.pdf
- Gatyas, G. (August 2011b). Top 20 Global Products, 2010, 10.08.2011, Available from http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-line%20Market%20Data/2010%20Top-line%20Market%20Data/Top_20_Global_Products.pdf

- Gomes, M. N., de Oliveira, C. M. A., Garrote, C. F. D., de Oliveira, V. & Menegatti, R. (2011). Condensation of Ethyl Cyanoacetate with Aromatic Aldehydes in Water, Catalyzed by Morpholine. *Synthetic Communication*, Vol.41, No.1, (January 2011), pp. 52-57, ISSN 0039-7911
- Guo, G., Arvanitis, E. A., Pottorf, R. S. & Player, M. P. (2003). Solid-Phase Synthesis of a Tyrphostin Ether Library. *Journal of Combinatorial Chemistry*, Vol.5, No.4, (January 2011), pp. 408-413, ISSN 1520-4766
- Hajipour, A. R. & Rafiee, F. (2010). Acidic Bronsted Ionic Liquids. *Organic Preparations and Procedures International*, Vol.42, No.4, (July 2010), pp. 285-362, ISSN 0030-4948
- Hangarge, R. V., Jarikote, D. V. & Shingare, M. S. (2002). Knoevenagel condensation reactions in an ionic liquid. *Green Chemistry*, Vol.4, No.3, (May 2002), pp. 266-268, ISSN 1463-9262
- Jenner, G. (2001). Steric effects in high pressure Knoevenagel reactions. *Tetrahedron Letters*, Vol.42, No.2, (January 2001), pp. 243-245, ISSN 0040-4039
- Knoevenagel, E. (1894). Ueber eine Darstellungsweise der Glutarsäure. *Berichte der Deutschen Chemischen Gesellschaft*, Vol.27, No.2, (Mai-August 1894), pp. 2345-2346, ISSN 0365-9631
- Kumar, H. M. S., Reddy, B. V. S., Reddy, P. T., Srinivas, D. & Yadav, J. S. (2000). Silica Gel Catalyzed Preparation of Cinnamic Acids Under Microwave Irradiation. *Organic Preparations and Procedures Int.*, Vol.32, No.1, (February 2000), pp. 81-83, ISSN 0030-4948
- Kumar, H. M. S., Subbareddy, B. V., Anjaneyulu, S. & Yadav, J. S. (1998). Non Solvent Reaction: Ammonium Acetate Catalyzed Highly Convenient Preparation of Trans-Cinnamic Acids. *Synthetic Communication*, Vol.28, No.20, (August 1998), pp. 3811-3815, ISSN 0039-7911
- Kuzemko, M. A., Van Arnum, S. D. & Niemczyk, H. J. (2007). A Green Chemistry Comparative Analysis of the Syntheses of (E)-4-Cyclobutyl-2-[2-(3-nitrophenyl)ethenyl] Thiazole, Ro 24-5904. *Organic Process Research & Development*, Vol.11, No.3, (June 2008), pp. 470-476, ISSN 1083-6160
- Laue, T. & Plagens, A. (2005). *Named Organic Chemistry*, John Wiley & Sons Ltd, ISBN 0-470-01040-1, Wolfsburg, Germany
- Li, C. & Chen, L. (2006). Organic Chemistry in Water. *Chemical Society Reviews*, Vol.35, No.1, (January 2006), pp. 68-82, ISSN 0306-0012
- Liese, A., Seelbach, K. & Wandrey, C. (2006). *Industrial Biotransformations*, WILEY-VCH Verlag GmbH & Co. KGaA, ISBN 3-527-31001-0, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany
- Li, J. J., Johnson, D. S., Sliskovic, D. R. & Roth, B. D. (2004). *Contemporary Drug Synthesis*, Wiley- Interscience, ISBN 0-471-21480-9, New Jersey, USA
- Lidström, P., Tierney, J., Wathey, B. & Westman, J. (2001). Microwave assisted organic synthesis – a review. *Tetrahedron*, Vol.57, No.45, (November 2001), pp. 9225-9283, ISSN 0040-4020
- Loupy, A. (2002). *Microwaves in Organic Synthesis*, WILEY-VCH Verlag GmbH & Co. KGaA, ISBN 3-527-30514-9, Weinheim, Germany

- Madivada, L. R., Anumala, R. R., Gilla, G., Alla, S., Charagondla, K., Kagga, M., Bhattacharya, A. & Bandichhor, R. (2009). An Improved Process for Pioglitazone and Its Pharmaceutically Acceptable Salt. *Organic Process Research & Development*, Vol.13, No.6, (December 2009), pp. 1190-1194, ISSN 1083-6160
- Martinez, C. A., Hu, S., Dumond, Y., Tao, J., Kelleher, P. & Tully, L. (2008). Development of a Chemoenzymatic Manufacturing Process for Pregabalin. *Organic Process Research & Development*, Vol.12, No.3, (June 2008), pp. 392-398, ISSN 1083-6160
- McCluskey, A., Robinson, P. J., Hill, T., Scottc, J. L. & Edwards, J. K. (2002). Green chemistry approaches to the Knoevenagel condensation: comparison of ethanol, water and solvent free (dry grind) approaches. *Tetrahedron Letters*, Vol.43, No.17, (April 2002), pp. 3117-3120, ISSN 0040-4039
- McNulty, J., Steere, I. J. A. & Wolf, S. (1998). The Ultrasound Promoted Knoevenagel Condensation of Aromatic Aldehydes. *Tetrahedron Letters*, Vol.39, No.29, (October 2000), pp. 8013-8016, ISSN 0040-4039
- Merrifield, R. K. (1963). Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide. *Journal of the American Chemical Society*, Vol.85, No.14, (July 1963), pp. 2149-2154, ISSN 0002-7863
- Mogilaiah, K. & Reddy, C. S. (2003). An Efficient Friedlander Condensation Using Sodium Fluoride as Catalyst in the Solid State. *Synthetic Communication*, Vol.33, No.18, (August 2003), pp. 3131-3134, ISSN 0039-7911
- Mogilaiah, K. & Reddy, G. R. (2004). Microwave-Assisted Solvent-Free Synthesis of trans-Cinnamic Acids Using Lithium Chloride as Catalyst. *Synthetic Communication*, Vol.34, No.2, (January 2004), pp. 205-210, ISSN 0039-7911
- Mukarram, S. M. J., Khan, R. A. R. & Yadav, R. P. (2007). Efficient Method for the Manufacture of (E)-Entacapone Polymorphic for a. United States Patent, 2007, Patent No: 0004935
- Okkerse, C. and van Bekkum, V. (1999). From Fossil to Green. *Green Chemistry*, Vol.1, No.2, (April 1999), pp. 107-114, ISSN 1463-9262
- Palmisano, G., Tibiletti, F., Penoni, A., Colombo, F., Tollari, S., Garella, D., Tagliapietra, S. & Cravotto, G. (2011). Ultrasound-enhanced one-pot synthesis of 3-(Het)arylmethyl-4-hydroxycoumarins in water. *Ultrasonics Sonochemistry*, Vol.18, No.2, (March 2011), pp. 652-660, ISSN 1350-4177
- Pratap, U. R., Jawale, D. V., Waghmare, R. A., Lingampalle, D. L. & Mane, R. A. (2011). Synthesis of 5-arylidene-2,4-thiazolidinediones by Knoevenagel condensation catalyzed by baker's yeast. *New Journal of Chemistry*, Vol.35, No.1, (November 2011), pp. 49-51, ISSN 1144-0546
- Rahmati, A. & Vakili, K. (2010). L-Histidine and L-arginine promote Knoevenagel reaction in water. *Amino Acids*, Vol.39, No.3, (June 2010), pp. 911-916, ISSN 0939-4451
- Ratan, C. (2007). Sunscreen compositions containing a UV-A sunscreen and photostablizers and antioxidants. United States Patent, 2007, Patent No: 0059258
- Ronga, L., Li, X., Wang, H., Shia, D., Tua, S., Zhuang, Q. (2006). Efficient Green Procedure for the Knoevenagel Condensation under Solvent-Free Conditions. *Synthetic Communication*, Vol.36, No.16, (September 2006), pp. 2407-2412, ISSN 0039-7911

- Roth, B. D. (1993). [R-(R*R*)]-2-(4-fluorophenyl)-beta, delta -dihydroxy-5-(1-methylethyl-3-phenyl-4[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, its lactone form and salts thereof. United States Patent, 1993, Patent No: 5273995
- Sheldon, R. A. (2007). The E Factor: fifteen years on. *Green Chemistry*, Vol.9, No.12, (December 2007), pp. 1273-1283, ISSN 1463-9262
- Sheldon, R. A., Arends, I. & Hanefeld, U. (2007). *Green Chemistry and Catalysis*, Wiley-VCH Verlag GmbH & Co. KGaA, ISBN 978-3-527-30715-9, Weinheim, Germany
- Smith, B. & March, J. (2001). *March's Advanced Organic Chemistry*, John Wiley & Sons Ltd, ISBN 0-471-58589-0, New York, USA
- Suslick, K. S. (1990). Sonochemistry, *Science*, Vol.247, No.4949, (March 1990), pp. 1439-1445, ISSN 0036-8075
- Tanaka, K. (2003). *Solvent-free Organic Synthesis*, WILEY-VCH Verlag GmbH & Co. KGaA, ISBN 3-527-30612-9, Weinheim, Germany
- Trost, B. M. (1991). The atom economy - a search for synthetic efficiency. *Science*, Vol.254, No.5037, (Dec 1991), pp. 1471-1477, ISSN 0036-8075
- Varma, R. S. (2002). Clay and clay-supported reagents in organic synthesis. *Tetrahedron*, Vol.58, No.7, (February 2002), pp. 1235-1255, ISSN 0040-4020
- Verdía, P., Santamarta, F. & Tojo, E. (2011). Knoevenagel Reaction in [MMIm][MSO4]: Synthesis of Coumarins. *Molecules*, Vol.16, No.6, (June 2011), pp. 4379-4388, ISSN 1320-3049
- Wada, S. & Suzuki, H. (2003). Calcite and fluorite as catalyst for the Knoevenagel condensation of malononitrile and methyl cyanoacetate under solvent-free conditions. *Tetrahedron Letters*, Vol.44, No.2, (January 2003), pp. 399-401, ISSN 0040-4039
- Walker, S. D., Borths, C. J., DiVirgilio, E., Huang, L., Liu, P., Morrison, H., Sugi, K., Tanaka, M., Woo, J. C. S & Faul, M. M. (2011). Development of a Scalable Synthesis of a GPR40 Receptor Agonist. *Organic Process Research & Development*, Vol.15, No.3, (March 2011), pp. 570-580, ISSN 1083-6160
- Wang, C., Guan, Z. & He, Y. (2011). Biocatalytic domino reaction: synthesis of 2H-1-benzopyran-2-one derivatives using alkaline protease from *Bacillus licheniformis*. *Green Chemistry*, Vol.13, No.8, (June 2011), pp. 2048-2054, ISSN 1463-9262
- Wasserscheid, P. & Welton, T. (2002). *Ionic Liquid in Synthesis*, WILEY-VCH Verlag GmbH & Co. KGaA, ISBN 3-527-30515-7, Weinheim, Germany
- Watson, T. J. N., Horgan, S. W., Shah, R. S., Farr, R. A., Schnettler, R. A., Nevill Jr, C. R., Weiberth, F. J., Huber, E. W., Baron, B. M., Webster, M. E., Mishra, R. K., Harrison, B. L., Nyce, P. L., Rand, C. L. & Goralski, C. T. (2000). Chemical Development of MDL 103371: An N-Methyl-D-Aspartate-Type Glycine Receptor Antagonist for the Treatment of Stroke. *Organic Process Research & Development*, Vol.4, No.6, (December 2000), pp. 477-487, ISSN 1083-6160
- Watson, T. J. N., Horgan, S. W., Shah, R. S., Farr, R. A., Schnettler, R. A., Nevill Jr, C. R., Weiberth, F. J., Huber, E. W., Baron, B. M., Webster, M. E., Mishra, R. K., Harrison, B. L., Nyce, P. L., Rand, C. L. & Goralski, C. T. (2000). Chemical Development of MDL 103371: An N-Methyl-D-Aspartate-Type Glycine Receptor Antagonist for the

Treatment of Stroke. *Organic Process Research & Development*, Vol.4, No.6, (December 2000), pp. 477-487, ISSN 1083-6160

Xia, Y., Yang, Z., Brossi, A. & Lee, K. (1999). Asymmetric Solid-Phase Synthesis of (3'R,4'R)-Di-O-cis-acyl 3-Carboxyl Khellactones. *Organic Letters*, Vol.1, No.13, (December 1999), pp. 2113-2115, ISSN 1523-7060

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Green chemistry is chemistry for the environment. It is really a philosophy and way of thinking that can help chemistry in research and production to develop more eco-friendly solutions. Green chemistry is considered an essential piece of a comprehensive program to protect human health and the environment. In its essence, green chemistry is a science-based non-regulatory and economically driven approach to achieving the goals of environmental protection and sustainable development. Combining the technological progress with environmental safety is one of the key challenges of the millennium. In this context, this book describes the environmentally benign approaches for the industries as well as chemical laboratories. In order to provide an insight into step change technologies, this book was edited by green organic chemists.

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