

Route of Knoevenagel Reaction from Conventional method to Greener methods

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Abstract: In the past few years, classic methods of synthesis have been replaced by newer methods of synthesis involving principles of Green Chemistry given by Anastas and Warner leading to environmentally safer products and processes and reducing pollution and thus making the environment greener. In this review article I have compared old classical method of Knoevenagel reaction with greener methods for a more sustainable, pollution free future society.

Key Words: Green chemistry, Knoevenagel reaction, solvent free reactions, sustainable chemistry, use of ultrasound radiations, catalysis, microwave chemistry and use of ionic liquids.

I. Introduction

The Knoevenagel [1] reaction is considered to be a modification of the aldol reaction [2]. It is named after Emil Knoevenagel. It is a condensation reaction of aldehydes or ketones 1 with active methylene compounds 2 in presence of base like ammonia or another amine or piperidine as a catalyst in organic solvents to yield α,β -unsaturated carbonyl compounds 3 (Fig. 1) which serve as intermediates in various reactions and compounds of medicinal interest [3-7]. Group attached to methylene group must be powerful enough to facilitate deprotonation to form enolate ion, even with a mild base.

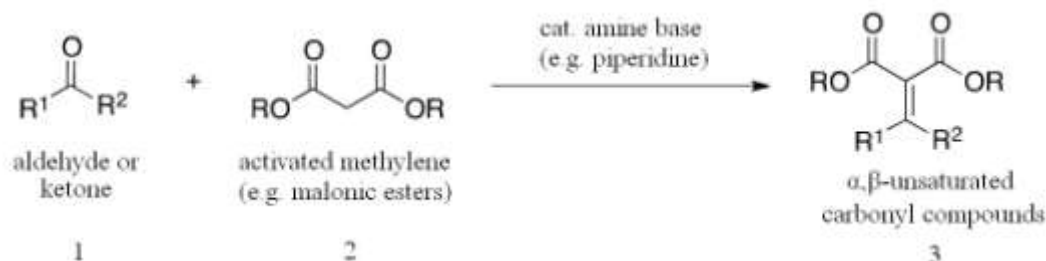


Fig. 1: Conventional method of Knoevenagel synthesis

II. Green Chemistry And New Synthetic Approaches

2.1 Ultrasound-catalysed Knoevenagel reactions

On application of high intensity ultrasound waves, acoustic cavitation usually occurs. Cavitation i.e. the formation, growth, and implosive collapse of bubbles due to high intensity sound waves triggers high-energy chemistry or is the driving force for sonochemistry [8]. It has been observed that ultrasound can greatly enhance chemical reactivity in a number of systems [9] effectively by exciting the atomic and molecular modes of the system (such as the vibrational, rotational, and translational modes).

Ultrasound irradiation [7] of piperonal 4 and malonic acid 5 was carried out at room temperature with pyridine as the solvent and piperidine as catalyst, Knoevenagel reaction product 6 was formed in 91.0% yield after three hours (Fig. 2) (McNulty et al., 1998). When same reaction is carried out under reflux conditions, after three hours, the product was formed in 52.0% yield.

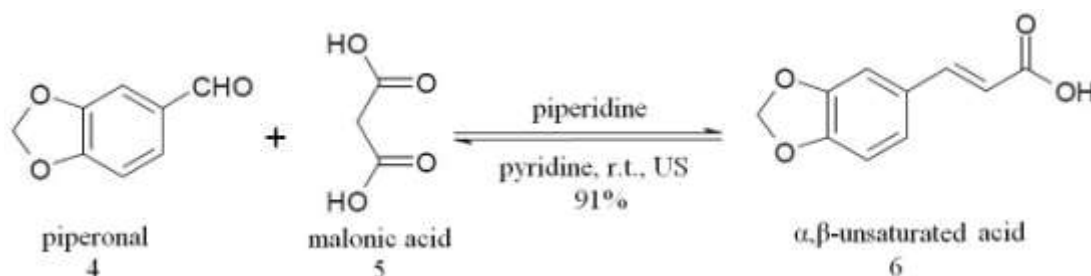


Fig. 2: Ultrasound catalysed Knoevenagel synthesis

Green Context:

- Room temperature and faster.
- Higher percentage yield.
- Use of ultrasound irradiation for activation.

2.2 The use of Microwave radiations in Knoevenagel reactions:

Traditionally, organic synthesis is carried out by heating with an external heat source which is a comparatively slow method as it depends on the thermal conductivity of materials. On the contrary, Microwaves act as high frequency radiations and generally heat any material such as polar molecules in a solvent or conducting ions in a solid with high efficiency and superheating becomes possible at ambient pressure. Thus a reaction that takes several hours under conventional conditions can be completed in few minutes.

2.2.1 Microwave-assisted ammonium formate -mediated Knoevenagel reaction

Ethyl 2-cyano-3-(4'-methoxyphenyl)-propenoate (Fig. 3) was obtained in 80% yield in pure form by irradiating mixture of p-anisaldehyde, ethyl cyanoacetate and ammonium formate (which were mixed in a round bottom flask fitted with CaCl₂ drying tube and placed on a bed of alumina taken in a beaker) in microwave for 90 seconds at 300 watts power level followed by intermittent cooling. The solid product, precipitated in a granular form, was filtered, washed well with water and dried and further purified by recrystallization from ethyl acetate-petroleum ether (m.p. of the product was 88 °C).

Yield: 1.8 g (80 %)

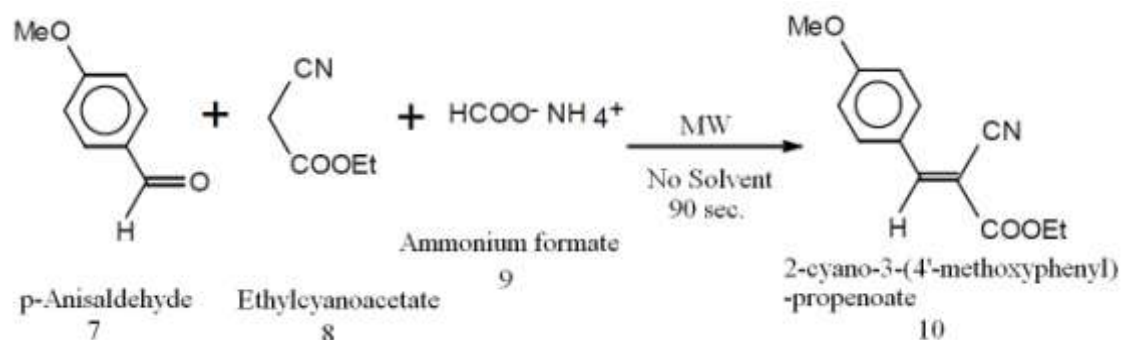


Fig. 3: Microwave-assisted ammonium formate -mediated Knoevenagel reaction

Green Context:

- □ Solvent-free reaction procedure
- Simple workup and rapid conversion (within 90 sec)
- Use of microwave energy for activation
- Higher percentage yield.

2.3 The use of ionic liquids in Knoevenagel reactions:

Recently interest has been developed in synthesis and use of Ionic Liquids (ILs) [10,11] due to their negligible vapour pressure which inhibits evaporation into the air as compared to other volatile organic chemicals (VOCs) and allows simple recycling and reuse in regards to Green Chemistry and alternative technologies. The pyrazolonic compound 13 was produced in 71.0% yield by carrying out reaction between benzaldehyde 11 and 3-methyl-1-phenylpyrazolin-5-(4H)-one 12, using ethylammonium nitrate as an ionic liquid [12] at room temperature (Fig. 4).

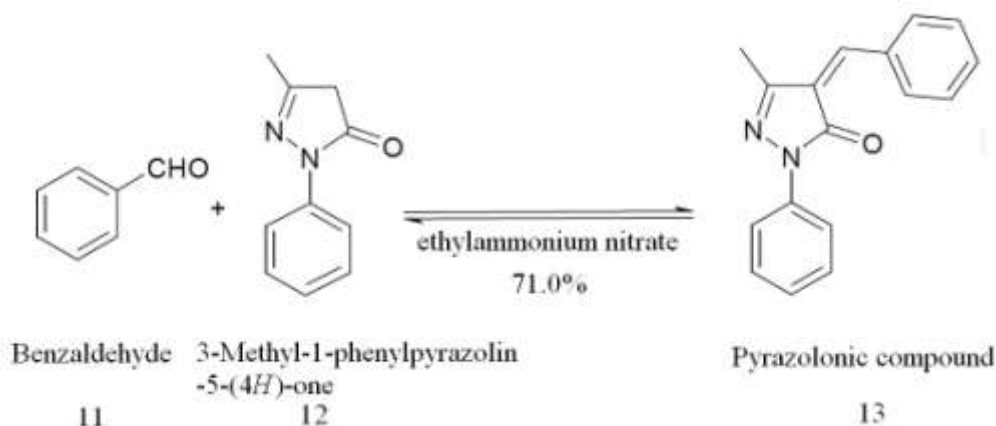


Fig. 4: Knoevenagel synthesis of Pyrazolinic compound using Ionic Liquid

Knoevenagel condensation is carried out in the presence of basic ionic liquid [13] 1-butyl-3-methylimidazolium hydroxide, [bmIm]OH as catalyst without use of any organic solvent. Ionic liquid efficiently catalyzes condensation of a wide variety of aliphatic and aromatic aldehydes and ketones with diethyl malonate, malononitrile, ethyl cyanoacetate, malonic acid and ethyl acetoacetate. The reactions are very fast and proceed at room temperature (Fig. 5).

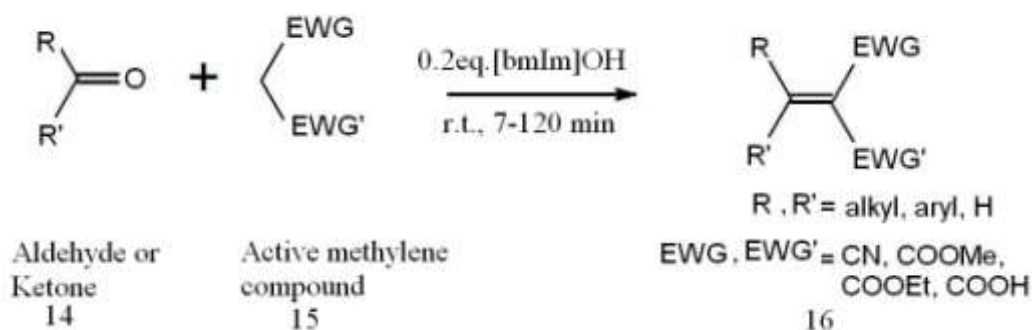


Fig. 5: Knoevenagel synthesis using Ionic Liquid

Green Context:

- Solvent-free reaction procedure
- Simple workup and rapid conversion
- Pollution free
- Room temperature and faster.

III. Conclusion

As illustrated by the reactions presented here, classic method of Knoevenagel condensation can be replaced by environmentally benign processes leading to formation of safer, pollution free products with higher yields in shorter duration of time making the environment green. These new processes have been useful in the development of more environmentally supportable products and chemical processes used in synthetic and pharmaceutical industry.

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