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Research Article

Solvent-Free Henry and Michael Reactions with Nitroalkanes Promoted by Potassium Carbonate as a Versatile Heterogeneous Catalyst

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The use of a simple weak inorganic base such as potassium carbonate facilitated the formation of carbon-carbon bonds through both the Henry and the Michael reactions with nitrocompounds. The application of this catalyst under environmentally friendly solventless heterogeneous conditions gave satisfactory to good yields of β -nitroalcohols, involving aliphatic and aromatic starting materials, as well as high to excellent yields in the formation of Michael adducts using several different Michael acceptors and nitroalkanes.

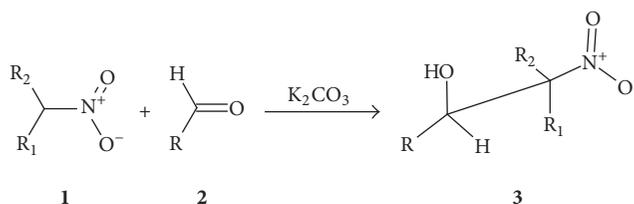
1. Introduction

The formation of a carbon-carbon bond can be carried out using various starting materials together with a vast amount of homogeneous or heterogeneous catalysts. Two important reactions which involve the synthesis of compounds through carbon-carbon bond formation include the Henry and the Michael reactions with nitroalkanes [1–3]. Under basic conditions nitroalkanes are able to deprotonate to form an intermediate compound known as the nitronate anion [4]. The nitronate anion can then react with aldehydes through the Henry reaction to yield β -nitroalcohols [5]. In the case of the Michael addition, the carbanion would react with Michael acceptors or α,β -unsaturated compounds to yield polyfunctionalised nitroderivatives [6].

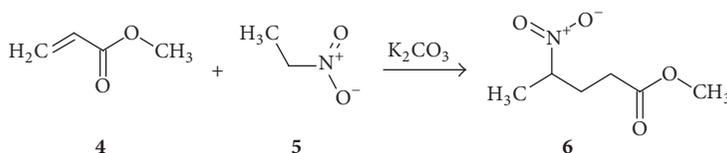
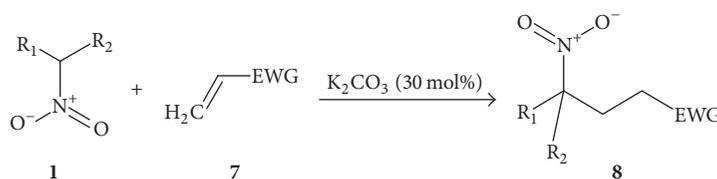
In recent years the nitroaldol and the Michael reactions were carried out using extensive catalysts, some of which containing complex structures. Various methodologies have been employed; however, in some cases, disadvantages of having such complex structures included applying either very low or substantially high temperatures to obtain the respective products at great yields [7–10]. A major drawback of some catalysts is that they resulted in the increased

formation of secondary products in these reactions. In the case of the nitroaldol reaction, the main side product is the formation of the nitroalkene through a further condensation reaction of the nitroalcohol. In some cases the use of certain catalysts resulted in the production of a conjugated enone through an aldol condensation side reaction, whereas some highly activated catalysts which were applied to the Michael addition were too reactive as reactions which resulted in the formation of the double addition products [4–6].

Herein, as a continuation of ongoing study on the development of environmentally friendly methodologies [11–13], our main interest in relation to this context was to identify a simple alternative and cheap heterogeneous solid catalyst useful for both the Henry and the Michael reactions, in accordance with moderate reaction conditions and the concept of Green Chemistry [14] to produce, respectively, β -nitroalcohols (Scheme 1) and polyfunctionalised nitroderivatives (Schemes 2 and 3) [15–17]. On this purpose potassium carbonate [18, 19] was identified as a suitable catalyst and produced average to good results for the nitroaldol reaction (Table 3) and good to excellent results for the Michael addition (Table 4). To the best of our knowledge, potassium carbonate was previously reported to catalyse only a few



SCHEME 1: The Henry (nitroaldol) reaction.

SCHEME 2: Michael addition model reaction using methyl acrylate and nitroethane with K_2CO_3 .SCHEME 3: Michael reactions using 30 mol% K_2CO_3 .

examples of Michael addition reactions, although never under neat conditions but with the required assistance of solvents [20, 21], ultrasounds activation, and ionic liquids [22], or with the use of a limited number of substrates as starting materials [23] or else not involving nitroalkanes but different nucleophiles [24–26].

2. Results and Discussion

In both reactions, the first part of the study consisted of the optimization screening through the investigation of some Henry (Table 1) and Michael reactions (Table 2) using potassium carbonate as the catalyst together with the variation of both physical and chemical conditions and without any solvent.

The Michael reaction was first investigated by performing a variety of trials using nitroethane (5) and methyl acrylate (4) as model reaction (Scheme 2).

Following these preliminary investigations, the Henry reaction gave good results when undergone at temperatures of $60^\circ C$, increasing the reaction rate substantially and using 10 molar% of catalyst (entry 5, Table 1). On the other hand, high temperatures were detrimental to the Michael additions as a second by-product was afforded, this most probably being the double Michael adduct. In order to decrease the formation of the bis-addition, the reaction temperature was kept at room temperature to promote increased formation of the desired monoaddition and together with the use of 30 molar% of catalyst the best result was obtained (entry 5, Table 2). These selected conditions were then employed in other Henry and Michael reactions in order to verify a more general applicability of the preliminary protocol, using

nitroalkanes and different aldehydes and α,β -unsaturated compounds, respectively.

As reported in Table 3, aliphatic aldehydes gave the best results in the least amount of reaction time while aromatic aldehydes with electron withdrawing substituents gave better yields than those containing electron donating groups. Parasubstituted aromatics were the most difficult substrates to react and when utilising 4-nitrobenzaldehyde a small amount of CH_2Cl_2 was required as the starting material was solid. In general average to good yields were obtained with this catalyst as the reaction itself is reversible [2] and thus it is difficult for it to reach completion. The major role played by the catalyst was that reactions only afforded in a selective way the nitroaldol product and no traces of any condensation side product were present.

The previous conditions were then applied to Michael reactions using different nitroalkanes and diversely functionalised Michael acceptors (Scheme 3) and the catalyst performed even better providing good to excellent product yields (Table 4). Only when using nitromethane were very low yields recorded, since the formation of the bis-addition side product was revealed due to the fact that it is a small and unhindered molecule, while using a secondary nitroalkane the temperature was increased to $60^\circ C$ as there is no possible formation of the bis-adduct. Also the results obtained from these trials indicated that 30 mol% of catalyst gave good yields at room temperature when using methyl acrylate as the Michael acceptor. However, reaction temperatures were increased to $60^\circ C$ and $90^\circ C$ when using cyclic and sterically hindered Michael acceptors like cyclic enones and *trans*-methyl crotonate in order to increase the speed of the reaction, whereas reactions which involved the use of

TABLE 1: Optimization of nitroaldol reaction using K_2CO_3 .

Entry	R	R ₁	R ₂	Mol (%) catalyst	Temperature (°C)	Time (h)	Yield ^a of 3 (%)
1	Ph	CH ₃	H	10	25	24	35
2	CH ₃	CH ₃	H	30	25	24	54
3	CH ₃	CH ₃	H	10	60	4	48
4	CH ₃ CH ₂ CH ₂	CH ₃	H	30	25	24	58
5	CH ₃ CH ₂ CH ₂	CH ₃	H	10	60	4	68

^aYield of pure isolated products.

TABLE 2: Optimization of Michael reaction using model reaction.

Entry	Mol % catalyst	Time (h)	Temperature (°C)	Yield ^a of 6 (%)
1	10	5	25	47
2	10	27 ^b	25, 60 ^b	50
3	20	24	25	58
4	10	7	60	54
5	30	7.5	25	60
6	30	48	25	61
7	30	6	50	58
8	30	7	35	55

^aYield of pure isolated product.

^bReaction was carried out at room temperature for 24 hours; temperature was increased to 60°C for 3 hours.

TABLE 3: Henry reaction using 10 mol% K_2CO_3 at 60°C.

Entry	R	R ₁	R ₂	Time (h)	Yield ^a of 3 (%)
a	CH ₃	CH ₃	H	4	48
b	CH ₃ CH ₂ CH ₂	CH ₃	CH ₃	5	46
c	CH ₃	H	H	4.5	75
d	Ph	CH ₃	H	4.5	60
e	CH ₃	CH ₃	CH ₃	4	48
f	PhCH ₂	<i>n</i> -C ₂ H ₅	H	5	50
g	CH ₃ CH ₂ CH ₂ CH ₂	<i>n</i> -C ₂ H ₅	H	4.5	60
h	PhCH ₂ CH ₂	<i>n</i> -C ₃ H ₇	H	6.5	58
i	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₃ H ₇	H	8	72
j	<i>p</i> -NO ₂ C ₆ H ₄	<i>n</i> -C ₄ H ₉	H	72	55 ^b
k	Ph	H	H	3.5	60
l	<i>c</i> -C ₆ H ₁₁	H	H	5	65
m	<i>p</i> -OCH ₃ C ₆ H ₄	H	H	24	60
n	<i>p</i> -NO ₂ C ₆ H ₄	H	H	4	66 ^b
o	CH ₃	Br	H	5	62

^aYield of pure isolated product.

^bReaction was carried out under CH₂Cl₂ solvent as the starting aldehyde was solid.

acrylonitrile required lower temperatures of 0°C to prevent immediate polymerization of acrylonitrile from occurring, which was evident through the formation of a thick yellow solid.

3. Conclusions

In summary, the utilisation of potassium carbonate in neat conditions is a very versatile and green synthetic method and

thus shows great applicability with a variety of substrates, containing different backbone structures, such as aliphatic straight chain and cyclic and aromatic compounds, to undergo both Henry and Michael reactions. Compared with the reported methods using expensive or unavailable organic catalysts, a common and inexpensive inorganic base (K_2CO_3) was here employed as the base catalyst. The presented reactions proceeded with complete regioselectivity providing the nitroaldol and Michael monoaddition products, respectively,

TABLE 4: Michael reactions with various nitroalkanes and Michael acceptors using 30 mol% K₂CO₃.

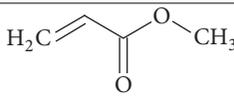
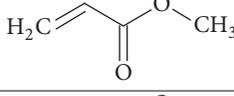
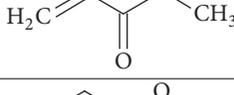
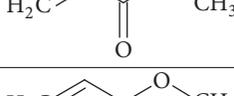
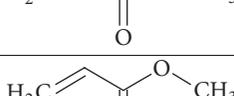
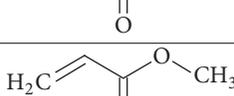
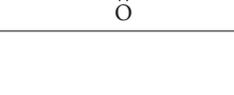
Entry	R ₁	R ₂	Michael acceptor	Michael adduct	Time (h)	Temperature (°C)	Yield ^a of 8 (%)
1	H	H		8a	24	25	30
2	C ₂ H ₅	H		8b	24	25	69
3 (i)	CH ₃	CH ₃		8c (i)	120	25	84
3 (ii)	CH ₃	CH ₃		8c (ii)	14	60	85
4 (i)	C ₃ H ₇	H		8d (i)	72	25	79
4 (ii)	C ₃ H ₇	H		8d (ii)	6	60	71
5	C ₅ H ₁₁	H		8e	21	25	66

TABLE 4: Continued.

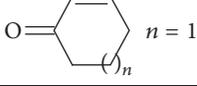
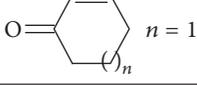
Entry	R ₁	R ₂	Michael acceptor	Michael adduct	Time (h)	Temperature (°C)	Yield ^a of 8 (%)
6 (i)	CH ₃	H	 <i>n</i> = 1	8f (i)	72	25	91
6 (ii)	CH ₃	H	 <i>n</i> = 1	8f (ii)	4	60	93
7 (i)	CH ₃	CH ₃	 <i>n</i> = 1	8g (i)	72	25	60
7 (ii)	CH ₃	CH ₃	 <i>n</i> = 1	8g (ii)	8	60	88
8 (i)	C ₂ H ₅	H	 <i>n</i> = 1	8h (i)	144	25	83
8 (ii)	C ₂ H ₅	H	 <i>n</i> = 1	8h (ii)	6	60	84
9	CH ₃	H	 <i>n</i> = 0	8i	3	60	92
10	C ₂ H ₅	H	 <i>n</i> = 0	8j	14	60	89

TABLE 4: Continued.

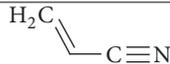
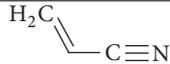
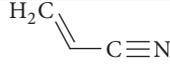
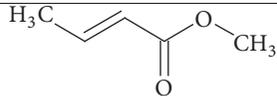
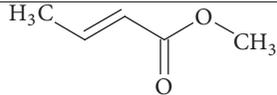
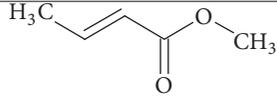
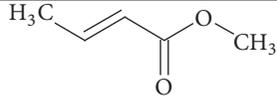
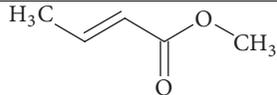
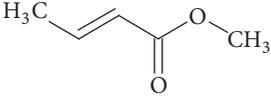
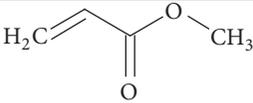
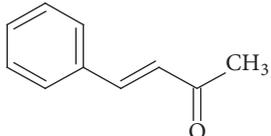
Entry	R ₁	R ₂	Michael acceptor	Michael adduct	Time (h)	Temperature (°C)	Yield ^a of 8 (%)
11	CH ₃	H		8k	2.5	0	62
12	CH ₃	CH ₃		8l	25	25	76 ^b
13	C ₂ H ₅	H		8m	4	25	57 ^b
14 (i)	CH ₃	H		8n (i)	24	25	Trace ^c
14 (ii)	CH ₃	H		8n (ii)	24	60	Trace ^c
14 (iii)	CH ₃	H		8n (iii)	10	90	47
15 (i)	C ₂ H ₅	H		8o (i)	24	25	Trace ^c
15 (ii)	C ₂ H ₅	H		8o (ii)	24	60	Trace ^c

TABLE 4: Continued.

Entry	R ₁	R ₂	Michael acceptor	Michael adduct	Time (h)	Temperature (°C)	Yield ^a of 8 (%)
15 (iii)	C ₂ H ₅	H		8o (iii)	24	90	59
16	COOCH ₃	H		8p	17	90	46
17	CH ₃	H		8q	12	60	48

^aYield of pure isolated product.

^bReactions were started at 0 °C for 1 hour to prevent acrylonitrile polymerization.

^cGC chromatograms revealed trace amounts of expected product.

^dCH₂Cl₂ was used as solvent as the starting acceptor was solid.

while tolerating many different functionalities. The common catalyst and the ready availability of the starting materials and the simplicity and versatility of the procedure and the valuable products make the protocol potentially practical and useful to synthetic chemists.

4. Experimental Section

4.1. General Information. All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR Spectrometer, calibrated against a 1602 cm⁻¹ polystyrene absorbance spectrum. Samples were either analysed as a thin film or in a Nujol™ mull, between sodium chloride discs. The ¹H- and ¹³C-NMR spectra were recorded on Bruker AM250 NMR spectrometer fitted with a dual probe at frequencies of 250 MHz and 62.9 MHz for ¹H and ¹³C NMR, respectively. An Aspect 3000 computer using 16 K complex points for ¹H NMR and 64 K complex points for ¹³C NMR was used for processing. Samples were dissolved in deuterated chloroform (with TMS): 5 mg in 0.8 mL CDCl₃ for ¹H NMR and between 35 mg and 50 mg in 0.8 mL CDCl₃ for ¹³C NMR. Reaction monitoring was done by TLC and GC analysis. Ready-purchased silica on PET sheets with fluorescent indicator, 254 nm, was used as stationary phase for TLC. Gas chromatography was carried out on a Shimadzu GC-2010 *plus* gas chromatograph equipped with a flame ionisation detector and HiCap 5 GC column with dimensions of 0.32 mm (internal diameter) × 30 m (length) × 0.25 μm (film thickness), using nitrogen as carrier gas. The synthesised compounds are known. Supplemental material (available online at <https://doi.org/10.1155/2017/6267036>) is available from the correspondence author.

4.2. Typical Procedure for the Nitroaldol Reaction and the Formation of 3-Nitro-2-butanol (3a). The nitroalkane, nitroethane (20 mmol), and the aldehyde, acetaldehyde (20 mmol), were mixed together. After thorough mixing, potassium carbonate (10 mol%) was added to the mixture. The reaction temperature was increased and monitored until it reached 60°C. Immediately after the reaction finished as observed from TLC, the catalyst was filtered off using a Grade 1 filter paper and dichloromethane as solvent. The solvent was evaporated and the crude product was purified by column chromatography using a mixture of cyclohexane and ethyl acetate giving (48%) of **3a** as 6:4 diastereomeric mixture: IR (neat): ν_{\max} 3421, 2985, 2943, 2910, and 1548, cm⁻¹ and ¹H NMR (250 MHz, CDCl₃) δ 1.24–1.3 (dd, *J* = 9.66 Hz, 3H), δ 1.54–1.59 (dd, *J* = 6.72 Hz, 3H), δ 2.26–2.40 (dd, *J* = 6.1 Hz, 1H), δ 4.08–4.22 (m, 0.6H), δ 4.32–4.42 (m, 0.4H), and δ 4.43–4.56 (m, 1H).

4.3. Typical Procedure for the Michael Reaction and the Formation of Methyl 4-Nitropentanoate (6). The nitroalkane, nitroethane (10 mmol), was mixed with the Michael acceptor, methyl acrylate (10 mmol). After through mixing, the potassium carbonate catalyst (30 mol%) was added to the mixture. Heating or cooling was applied only when required,

according to starting materials (Table 4). The reaction was left standing for the appropriate time. The catalyst was then filtered using a small column fitted with cotton and Florisil. The filtrate was then evaporated in vacuo and the crude product was purified via column chromatography using a mixture of cyclohexane and ethyl acetate affording the pure **6**: IR (neat): ν_{\max} 3001, 2956, 2850, 1732, and 1556 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 4.74–4.59 (m, 1H), δ 3.70 (s, 3H), δ 2.45–2.01 (m, 4H), and δ 1.59–1.54 (d, 3H, *J* = 6.72 Hz); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.4, 82.4, 51.9, 30.0, 29.9, and 19.3.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

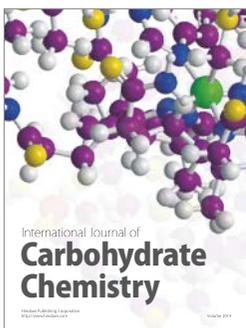
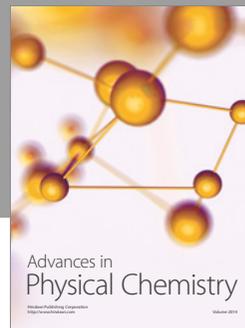
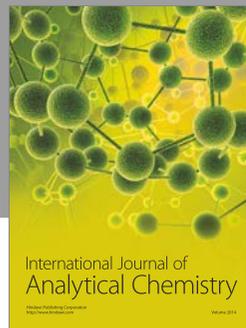
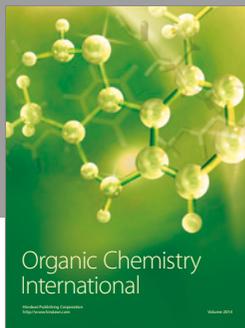
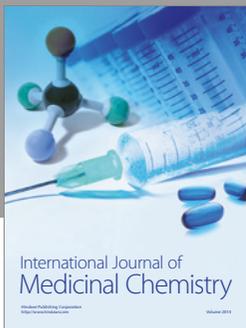
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