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ADDITION OF MASKED ACYL ANION TO α, β UNSATURATED ESTER IN SYNTHESIS OF 4-, 5-, 6- KETO CARBOXYLIC ESTERS

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In this paper, a novel one-pot synthesis of 4-,5-,6– keto carboxylic esters were developed using Michael's addition of masked acyl to α, β- unsaturated esters. We first developed an efficient and general one-pot method for two carbon-carbon bond formation to prepare α, β- unsaturated esters with high regio and stereoselectivity with good yield in less reaction time.

Keywords: Michael addition, enolate, acyl anion, chelation, benzylation, keto carboxylic

1. Introduction

Michael addition is one of organic synthesis's most efficient and vital carbon-carbon bond-forming reactions [1, 2]. In particular, they are atom-efficient procedures [3] and thus inherently green transformations [4]. Michael addition reaction of electron-deficient alkenes has been used to produce defunctionalized synthons that have been extensively used in organic synthesis [5-8]. The commonly employed anionic alkyl synthons for Michael addition are those derived from nitroalkanes [9], ethyl cyano carboxylates [10], malonates (11), α-nitro esters [12] and ter-butylglycinates [13]. Such Michael donors have been extensively studied, and their limitations, such as the requirement of excess nitroalkanes, restriction in the type of Michael accepters tolerated and low to moderate yield of the product, are encountered. 3-substituted-α, β-unsaturated aldehyde gives predominantly 1,2-addition with secondary nitroalkanes and β-nitro alcohols [14]. Undesired multi-additions are observed in Michael's addition of nitroalkane anions. The use of masked acyl anion equivalents in forming carbon-carbon bonds has been proven to be a powerful strategy for developing new synthetic methods. It has been used to

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add aldehydes to the addition of α-aryl-4-morpholenoacetonitrile [17-18] to ethyl acrylate followed by hydrolysis of masked acyl function is a helpful method for synthesizing ethyl 4-oxo-4- phenylbutanoate [19-20]. α-aminonitriles are useful synthons in the synthesis of alkaloids, dienamine [21] and amides [22].

The other masked acyl anion, like dithians, has been used in conjugate addition [23].

The synthetic multistep procedure for synthesizing two carbon-carbon bonds in one pot needs to be better reported among the growing number of methodologies developed during recent years for green transformation. The strategy of carbon-carbon bond formation under the same reaction condition is of practical interest. Such methods may depend on several factors such as (a) ready availability of utilized substrate, (b) regio and stereoselectivities of the process, (c) simplicity of experimental procedure, and (d) eventual possibilities of enantioselective construction of natural products or intermediate leading of natural products. We recently investigated the utilization of morpholino-phenylacetonitriles as acyl anion equivalents in the synthesis of γ-keto acids under primary conditions at room temperature [27]. α-alkylated-γ-keto esters were prepared by Michael addition of morpholino-phenylacetonitriles to α, β-unsaturated esters and the enolates generated in situ were alkylated with allyl bromide in one pot three component process. Morpholinoacetonitriles can easily be prepared at room temperature, are stable and can be stored for a long time [28]. Its anion can be generated easily and alkylated at room temperature in the presence of dry potassium hydroxide in dimethyl sulphoxide [29]. We have been interested in developing an efficient and general method for the preparation of 2-substituted γ-keto esters. It could provide a common precursor for synthesizing many natural products such as dihydro naphthalene, cyclopentanone, pyrrolidine, etc. [30-37].

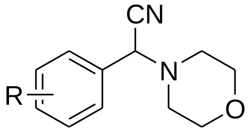
This paper represents preliminary reports of our new approach to the synthesis of α-benzyl-γ-ketoacid, δ-ketoacid and 2 or 3 substituted-4-carbomethoxy-6-keto hexanoic esters. Based on the conjugate addition of morpholino-phenylacetonitrile and subsequent alkylation of enolates by benzyl chloride and electron-deficient alkenes electrophiles, afford selectively single major product by 1,4 addition and no 1,2 addition product formed. Due to the preferential chelation of the enolate, the high regio and stereoselectivity were accounted in the reaction. In the present protocol, the generation of anion, Michael addition, enolate alkylation, and deprotection of the carbonyl group are carried out in one pot under similar conditions, making this approach a very attractive feature.

2. Result and Discussions

The morpholino-phenylacetonitriles were prepared from the corresponding arylaldehyde using a literature procedure [17]. The aryl aldehyde solution in methanol was stirred with morpholine hydrochloride, and an equivalent amount of sodium cyanide yielded morpholino-phenyl acetonitrile in high yield. Results of the conversion of aldehyde to morpholino-phenyl acetonitrile are summarized in Table 1.

The anion of morpholino-phenyl acetonitrile enolates is used in various organic reactions to synthesise bioactive compounds. [36, 37] Here, the anion of morpholino phenylacetonitriles was generated by the treatment of a solution of dimethyl sulphoxide with dry potassium hydroxide at room temperature. The conjugate addition of anion of morphonitrile to methylacrylate at room temperature was followed by quenching benzyl bromide to yield 2-benzyl esters, which on acidic workup gave α-benzyl-γ-keto esters. The results of this tandem conjugate addition enolate alkylation reaction to γ-ketoacids Table 2 entries 3(a-d) are summarized in Scheme 1. The reaction proceeded smoothly and produced the desired α-benzyl-γ-keto ester. In low yields, two stereoisomers were obtained. After optimizing the reaction condition by varying the temperature and solvent, the reaction was completed, and the desired product yielded 68-81%. Using benzyl bromide for benzylation of enolates 2 increased the conversion to 92% yield. The preferential chelation of the enolate 2 accounts for high regio and stereoselectivity in the formation of α-benzyl-γ-keto esters.

The influence of the solvent on the product formation was observed during benzylation. The diethyl ether and dichloromethane did not give any desired result, whereas the use of THF resulted in the formation of other products, namely benzylmorpholine amides and benzylacrylate, in various amounts. The formation of benzylmorpholine could be explained by the presence of oxygen traces from the air, and its formation was avoided using dimethylsulphoxide as a solvent. Finally, a mixture of THF and DMSO with a ratio of 2:8 was chosen for further studies. The excess of THF may result in the formation of lachrymatic benzylacrylate in a smaller proportion. Its formation was avoided when the reaction was carried out at 0 ˚C temperature and a small amount of DMSO with more excellent selectivity and higher yield. The NMR spectra showed various characteristic peaks. We established stereo and regio-controlled Michael addition and subsequent benzylation, so we focused on the alkylation of α-position. We performed the quenching of enolate **2**, in which R_2=H and R_1=Et, with ethyl chloroacetate, under the same reaction condition established for the benzylation step. The reaction proceeds smoothly and produces the desired product with a 40-50 % yield. The use of ethyl bromoacetate increases the yield of the reaction from 55 to 64 % [Scheme 1], and the results are summarized in Table 2 entries (4a-4d). To generalise the reaction, an equivalent of methyl acrylate was used for the alkylation of enolate 2, and it proceeded smoothly, and 6-ketoester formed in 50-60 % yield [Scheme1]. All these results are summarized in Table 2 entries (5a-5d). In the formation of 6-keto ester, various alkene electrophiles were used for sequential Michael addition reaction. The reaction of enolate 2 with N-bromosuccinamide was examined for preparation of α-bromo-γ-keto acids. Surprising results were obtained by applying NBS. The unexpected Michael addition product was observed instead of the α-brominated derivative. Then, influences of NBS were examined for sequential Michael addition reaction to the enolate solution. The solution of NBS in dimethylsulphoxide was stirred for 12 hrs.



X

Table 1

Synthesis of α-morpholino-phenylacetonitriles

R in Compound (X)	Yield (%)	M.P [17] (˚C)	IR Analysis (cm^{-1})	^{1}HNMR Analysis
H	72	61-62	1501, 1608, 2234	2.8δ(s,4H),3.8δ(s,4H), 4.8δ(s,1H), 7.3 - 7.5δ(m,5H).
4-OMe	75	64-65	1502, 1608, 2244	2.75δ(s,4H),3.8δ(s,4H),3.9δ(s,3H), 4.8δ(m,1H).
3,4-$(OMe)_2$	78	78-79	1501, 1600, 2238	2.8δ(s,4H), 3.76δ(s,4H),3.9δ (s,,6H), 4.8δ(s,1H).
4-Cl	64	190-192	1507, 1608, 2224	2.72δ(s,4H),3.83δ(s,4H),4.8δ(s,1H).
4-NO_2	53	133-135	1503, 1608, 2234	2.8δ(s,4H),3.78δ(s,4H),4.8δ(s,1H), 7.4δ(d,2H),8.10δ(d,2H).

The reaction was followed by using TLC. As the reaction of NBS to morpholino-phenyl acetonitrile increases, the formation of γ-keto acids Table 2 (entry 3a) and the formation of hexanoic acid Table 2 (entry 5a) decreases. While keeping the quantity of NBS two moles and increasing the quantity of methyl acrylate from 2.5 to 3.5, there is a change in the formation of 6-keto acids Table 2 (entry 5a). Compound 5a 1HNMR analysis shows a clear multiplate for CH group at 3.54 ppm. While CH_2 at 5 position doublets of doublet for two H, it shows no separation between two protons of CH_2. This NMR clearly explains the stereo selectivity of the compound.

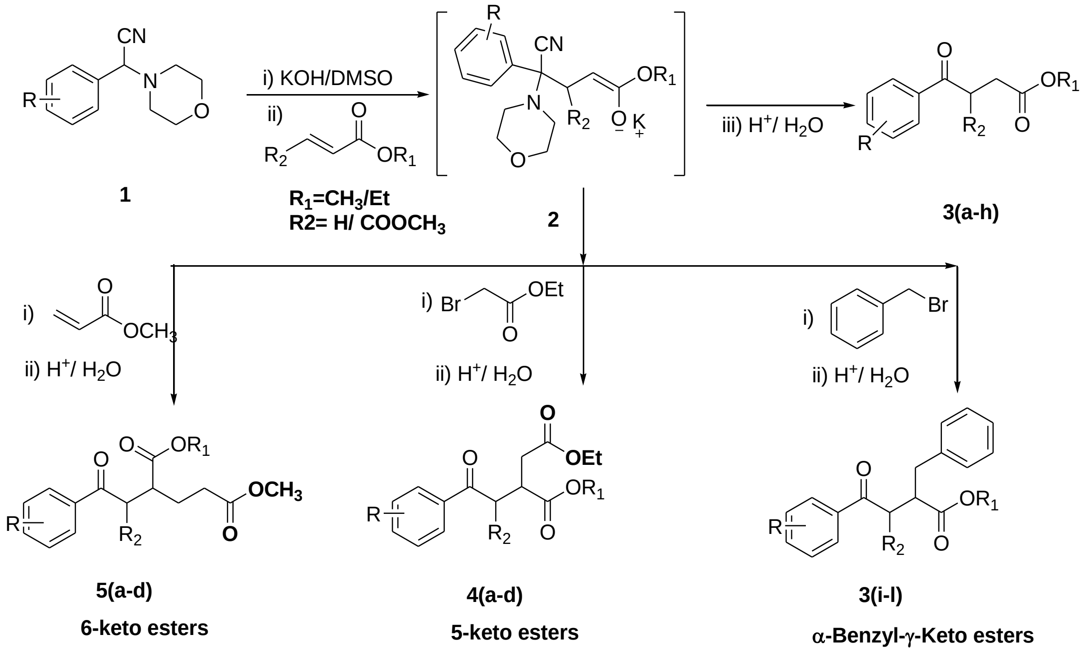
We took advantage of our finding concerning the high selectivity in Michael's reaction of morpholino-phenyl acetonitrile carbanion with open-chain methylmethacrylate.

Table 2

Synthesis of keto esters

Compound	R	R_1	R_2	Yield (%)
3a	H	$-CH_3$	H	90
3b	4-OMe	$-CH_3$	H	92
3c	3,4-$(OMe)_2$	$-CH_3$	H	85
3d	4-Cl	$-CH_3$	H	89
3e	H	$-CH_3$	$-COOCH_3$	87
3f	4-OMe	$-CH_3$	$-COOCH_3$	93
3g	3,4-$(OMe)_2$	$-CH_3$	$-COOCH_3$	91
3h	4-Cl	$-CH_3$	$-COOCH_3$	84
3i	H	$-CH_3CH_2$	H	65
3j	4-OMe	$-CH_3CH_2$	H	61
3k	3,4-$(OMe)_2$	$-CH_3CH_2$	H	67
3l	4-Cl	$-CH_3CH_2$	H	59
4a	H	$-CH_3CH_2$	H	64
4b	4-OMe	$-CH_3CH_2$	H	62
4c	3,4-$(OMe)_2$	$-CH_3CH_2$	H	68
4d	4-Cl	$-CH_3CH_2$	H	61
5a	H	$-CH_3$	H	51
5b	4-OMe	$-CH_3$	H	56
5c	3,4-$(OMe)_2$	$-CH_3$	H	62
5d	4-Cl	$-CH_3$	H	55

Because of intramolecular bridging in the enolate was assumed to enhance facial selectivity. We indeed found high selectivity in the Michael addition of morpholino-phenyl acetonitrile carbanion to methyl acrylate and subsequent benzylation of enolate. Moreover, the alkylation of enolate 2 by methyl acrylate afforded single stereoisomers as out of two possible isomers was formed it determined by NMR analysis of crude product.



Sheme 1: Synthesis of 4-, 5-, 6- keto carboxylic esters

The tandem Michael addition alkylation procedure allows easy variation at α-carbon atom and allows assembly of the 4-, 5-, 6-keto carboxylic ester. The enantiomerically pure 2-benzyl 4-keto esters were prepared using this method.

3. Experimental Section

All melting points or boiling points were determined to indicate oil-bath temperature. IR spectra were determined on a Perkin-Elmer spectrometer model 1615. ^{1}H NMR spectra were determined for all compounds reported in Varian spectrometer (300 MHz) in $CDCl_3$. Mass spectra (GCMS) were recorded on a Shimadzu Q 5050 instrument. The progress of the reaction was checked by TLC analysis. The analytical value of C, H, and N for all compounds was observed and calculated.

4. Preparation of the α-aminonitriles [17]

The aldehyde (0.05 moles) in a minimum of MeOH was added over 1 h to a solution of the morpholine hydrochloride (0.05 moles) and NaCN (0.06 moles) in H_20 (10 ml). The solution was stirred at 30° for 4 h, quenched with water and extracted into ether. The combined ether extracts were washed with water, saturated sodium metabisulphite solution and water. After drying over sodium sulphate, the ether extracts were evaporated to afford the α-aminonitriles as pale yellow oils.

5. General Procedure: Preparation of γ-keto esters [3a-3h]

A solution of α-aryl-4-morpholineacetonitrile (10 mmole) in DMSO was added drop wise to KOH (10 mmole) solution in DMSO at 0° C with constant stirring for 30 min. Methyl acrylate / diethyl maleate (12 mmole) in DMSO was added to solution at 0° C and stirring continued for 2-3 hrs at room temp. After the complete disappearance of the stirring material, the reaction mixture was acidified with (2*N*) HCl. The product was extracted in diethyl ether (2 X 10 ml), washed with brine, dried over ($MgSO_4$) and concentrated. The residue was purified by column chromatography [silica gel, eluent hexane: ethyl acetate (9:1)] to give compound 3a-h.

(3a) IR (nujol): λmax 1736, 1661, 1600,1500 cm^{-1}; ^{1}H NMR δ 2.86(t, 2H, J=6Hz), 3.28(t, 2H,J=6Hz),3.72(s,3H),7.44(t,2H,J=5.3Hz), 7.56(d,1H,J=3.3Hz), 7.95(d,1H,J=8.2Hz); ^{13}CNMR:198.18(s), 177.2(s), 137.48(s), 132.4(s), 128.9(s), 50.6(s), 33.49(s), 29.82(s); MS (m/z): 51,77,87,105,192(M^{+}).

(3e) IR (nujol): λmax 1734, 1681, 1600,1500 cm^{-1}; ^{1}H NMR δ 3.06(dd, 2H, J = 1.5,7.2Hz), 3.68(s,3H), 3.69(s,3H), 4.86(t,1H, J=7.2Hz), 7.46(m,5H); ^{13}CNMR:198.8 (s),179.2 (s), 132.8(s), 128.85(s), 50.9(s), 50.3(s), 28.7(s).

(3i) IR (nujol): λmax 1736, 1678, 1601,1507 cm^{-1}; ^{1}H NMR δ 2.78 (t, 1H, J = 6.6Hz), 3.28(t, 1H, J=6.6Hz), 3.66(m,4H), 3.89(s,3H), 5.18(d,2H, J=9.3Hz), 6.95(d,2H, J=7.5Hz), 7.35(s, 5H), 7.96(d, 2H, J=7.5Hz).

6. General Procedure: Preparation of 5 or 6-keto esters

A solution of α-aryl-4-morpholineacetonitrile 1 in DMSO (10 mmole) was added drop wise to KOH (0.12g :10 mmole) in DMSO at 0° C and stirring was continued for an additional 30-40 min. Methyl acrylate (12 mmole) in DMSO was added to solution at 0° C and stirring continued for 2-3 hrs at room temperature. Then benzyl bromide (15 mmoles) solution in DMSO was added drop wise in the reaction mixture and stirring material for about 20-30 hrs. The progress of reaction was followed by TLC. The reaction mixture was acidified with (2*N*) HCl. The product was extracted in ether and (2 X 10 ml), washed with brine, dried over ($MgSO_4$) and solvent evaporated to concentrate. Residue was purified by column chromatography [silica gel, eluent hexane: ethyl acetate (9:1)] to give compound 3i-l.

(4a) IR [Neat]: λmax 1735, 1677, 1600,1576, 1507 cm^{-1}; ^{1}H NMR δ 1.27(t, 3H, J = 6Hz), 2.72-2.78(m,1H), 3.01-3.07(m,1H), 3.27-3.30(m,1H), 3.67(s,3H), 3.706(d,2H, J=8Hz), 4.18 (q, 2H, J = 6Hz), 6.93(dd, 2H, J=6.5Hz),7.95 (dd,2H, J=6.5Hz).

(5a) IR [Neat]: λmax 1736, 1678, 1600,1511 cm^{-1}; ^1H NMR δ 1.94-2.2(m, 2H), 2.433(t,2H, J=6.9Hz), 3.09(dd,2H, J=5.4Hz), 3.54(m,1H), 3.68(s,3H), 3.711(s,3H), 7.46 (t, 2H, J = 7.5Hz), 7.62(d, 1H, J=7.5Hz), 7.95 (d,2H, J=7.5Hz).

7. Conclusion

A series of novel 4-,5-,6- keto carboxylic esters were synthesized via Michael addition reaction with less reaction time and characterized by NMR and FT-IR spectroscopy. We established a novel stereo and regio controlled Michael addition and subsequent benzylation. We observed high regio and stereoselectivity in the formation of α-benzyl-γ-keto esters. The present tandem Michael addition-alkylation procedure allows easy variation at α-carbon atom and allows assembly of the 4-, 5-, and 6- keto carboxylic ester.

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