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# Rapid and Simple Method of Monoacylation of Polyols by β-Ketoesters Using Microwave Irradiation

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**Abstract:** Polyols undergo rapid selective transesterification with  $\beta$ -ketoesters upon microwave irradiation in solvent-free and catalyst-free conditions to form monoesters.

Keywords:  $\beta$ -Ketoesters, microwaves, monoesters, polyols, solvent- and catalyst-free reactions

### INTRODUCTION

Fatty acid monoglycerides (MG) find widespread use in the food, cosmetic, agro and pharmaceutical industries.<sup>[1,2]</sup> These molecules are used as emulsifiers<sup>[1]</sup> and as starting materials for numerous synthetic applications,<sup>[2]</sup> for example, in the synthesis of phospholipids, defined triacylglycerols, and glycolipids. Other monoesters of glycerol, more specifically esters of  $\beta$ -keto esters, have been shown to promote absorption of insulin and inulin<sup>[3a,3b]</sup> in rabbits and enhance drug absorption in the intestine.<sup>[3c,3d]</sup>

Esters of alcohols can be formed by esterification or more conveniently by transesterification.<sup>[4]</sup> The monoesterification of 1, *n*-diols can be achieved by careful control of reaction conditions,<sup>[5]</sup> continuous extraction,<sup>[6]</sup> the use of alumina as a support,<sup>[7]</sup> phase-transfer catalyst,<sup>[8]</sup> inorganic polymer

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supports,<sup>[9]</sup> or via the formation of cyclic compounds.<sup>[10,11]</sup> The other methods for selective acylation of polyols include the use of catalysts such as metal sulfates supported on silica gel,<sup>[12,13]</sup> silica gel,<sup>[14]</sup>  $Al_2O_3/MeSO_3H$ ,<sup>[15,16]</sup> and organotin reagents.<sup>[17,18]</sup> The esters used in these studies were ethyl propionate, ethyl ethanoate, methyl butanoate, methyl pentanoate,<sup>[12,13]</sup> and alkenyl ester.<sup>[18]</sup>

Numerous methods for transesterification of  $\beta$ -ketoesters have been reported<sup>[19]</sup> but selective monoacylation of polyols with  $\beta$ -ketoesters still remains a challenge. 2-Mercaptoethanol and 2-amino-2-methyl-1,3-propanediol show selective transesterification with  $\beta$ -ketoesters in the presence of NBS  $(N-Bromo Succinimide)^{[19a]}$  and Yttria-Zirconia-based Lewis acid catalyst<sup>[20]</sup> to form the corresponding ester and amide. However, no selectivity was observed when  $\beta$ -ketoesters were transesterified with ethylene glycol in the presence of NBS, which yielded only the diester, while Yttria-Zirconiabased monoacylation of 1, 2-propanediol does not address the question of selectivity at all. The reaction of ethyl acetoacetate with glycerol in the presence of natural kaolinitic clay<sup>[19b]</sup> yields only the diacylated product (55%). Even though aromatic  $\beta$ -ketoesters could be transesterified in the presence of H $\beta$ -zeolite,<sup>[19c]</sup> the reaction occurs only at the secondary alcohol and not at the primary alcohol group. Commercially available neutral chromatographic alumina<sup>[19d-g]</sup>-mediated transesterification of  $\beta$ -ketoesters with 1,2- or 1,3-diols fails to give the monoacylated product. All these methods use "green catalysts" (viz. kaolinitic clay,  $H\beta$ -zeolite, alumina) for the acylation of glycerol and diols, but none of them are selective for the monoacylated product. Clearly there was a need to develop a method for the selective monoacylation of glycerol with  $\beta$ -keto esters.

This article reports the monoacylation of glycerol with a wide range of  $\beta$ -ketoesters using microwave irradiation.<sup>[21]</sup>

#### **EXPERIMENTAL**

A domestic microwave (980 Watt) oven was used (Batliboi Eddy, India) and operated at Power 4 of total power 9. <sup>1</sup>H NMR spectra were recorded using Bruker 400 MHz and <sup>13</sup>C NMR spectra were recorded using a Bruker 100 MHz Instrument. Mass spectra were recorded using micromass Quadrupole Time-of-fight (Q-tof) mass spectrometer.

 $\beta$ -ketoesters were purchased from Sigma-Aldrich Co., USA. Polyols and solvents were purchased locally and all solvents were distilled before use.

## **General Procedure of Synthesis of Compounds**

15 mmol of glycerol (1.38 g) and 3 mmol (390 mg) of ethyl acetoacetate was put in a test tube, placed in an  $Al_2O_3$  bath, and irradiated by Microwave

#### **Monoacylation of Polyols**

Irradiation (MW). The progress of the reaction was followed by TLC. After the completion of the reaction, the reaction mixture was dissolved in ethyl acetate and washed with saturated brine. Solvent was evaporated and the product was purified by column chromatography. The monoacyl glycerol of acetoacetic acid was obtained as a colorless oily liquid. Yield 80% (425 mg). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  (ppm) 2.22 (s, 3H), 3.33–3.36 (m, 2H), 3.59 (s, 2H), 3.63–3.65 (m, 1H), 3.92–3.96(dd, 1H), 4.07–4.11(dd, 1H), 4.67–4.70 (t, 1H), 4.93–4.95 (d, 1H). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 400 MHz)  $\delta$  (ppm) 29.9, 49.7, 62.4, 66.1, 69.1, 167.2, 201.6. EIMS (m/z = 199.14 (M + Na)<sup>+</sup>, 100%).

#### **RESULTS AND DISCUSSION**

In a typical experimental procedure, when  $\beta$ -keto esters were treated with polyols under microwave irradiation, the corresponding monoesterified product was obtained in good to excellent yields (63–92%) (Scheme 1). The reaction proceeded smoothly under microwave irradiation probably because of the efficient absorption of microwave energy by the polar reactants that promote the reaction. Diacylglycerol is the minor product (5–15%). Transesterification of ethyl acetoacetate with glycerol was taken as a model reaction. The molar ratio of ethyl acetoacetate–glycerol affects product distribution and can be controlled to maximize the yield of monoacyl glycerol (80%). For a molar ratio of 1:1 (glycerol–ethyl acetoacetate), 60% of the corresponding monoglyceride and 25–27% of the 1,3-diglyceride were obtained. When the molar ratio was increased to 1:5 (ethyl acetoacetate–glycerol), the



Scheme 1.

formation of monoacyl product increased to 80% and only 5% of diacyl glycerol was obtained. No further improvement in the conversion to monoacylglycerol was seen upon increasing the ethyl acetoacetate to glycerol ratio. Complete elimination of the diacylglycerol formation was difficult even by additional optimization of power and time of the reaction. This could be because the concentration of the monoacyl glycerol increases with time as compared to glycerol and it starts getting diacylated. The minor amount of diacylated product was removed by column chromatography. Acyl migration has been reported in the regioselective acylation of 1,3-diacylglycerol is lower than that of 1-monoacylglycerol, the latter being more prone to acyl migration.<sup>[22]</sup> In the case of 1-monoacylglycerols reported here, this trend of acyl migration was observed as indicated by <sup>1</sup>H NMR and TLC. The acyl migration of pure 1-monoglycerides is more pronounced in the slightly acidic CDCl<sub>3</sub>-TMS than in DMSO-d<sub>6</sub>.

In the cases of ethyl acetoacetate (Table 1, entry 5), methyl acetoacetate (Table 1, entry 4), and ethyl-4-nitrobenzoyl acetate (Table 1, entry 3), good yields (75–80%) of the corresponding monoacyl glycerol were obtained within 4 min. However, ethyl-4-methoxybezoyl acetate (Table 1, entry 2) and ethyl benzoyl acetate (Table 1, entry 1) required a marginal increase in the reaction time (5 min) for yields of 73-75%. When *iso*-propyl acetoacetate (Table 1, entry 6) and *tert*-butyl acetoacetate (Table 1, entry 7) were transesterified with glycerol, the reaction time was 6 and 7 min respectively and the yields were only 63-65%. It is important to note that in uncatalyzed transacetoacetylation, *tert*-butyl acetoacetate does not react with diols and triols to give the monoacylated product.<sup>[19d]</sup>

Ethylene glycol reacts with various  $\beta$ -ketoesters (Table 1, entries 8–11) to form the corresponding monoesters in excellent yields (82-92%) in 8-14 min. Significantly, the NBS-catalyzed transesterification of  $\beta$ -ketoesters with ethylene glycol did not result in any monoacylated product.<sup>[19a]</sup>  $\beta$ -Ketoesters undergo selective transesterification with diethylene glycol (Table 1, entries 12-16) to give the corresponding monoester in excellent yields (80-92%), suggesting that the presence of the oxygen atom in diethylene glycol has no bearing on the monoacylation. However, a decrease in reaction time was observed during the transesterification of  $\beta$ -ketoesters with diethylene glycol as compared to ethylene glycol, and the yields were nearly the same for the monoacylated products of both ethylene glycol and diethylene glycol. 1,4-Butenediol (Table 1, entry 19) undergoes monoesterification with benzoyl acetoacetate in 8 min with 85% yield whereas 1,4-butane diol (Table 1, entry 17) and 1,5-pentane diol (Table 1, entry 18) were transesterified with benzoyl acetoacetate to form the corresponding monoacylated products in 7 min. Thus, this method is potentially applicable for selective acylation of both saturated and unsaturated diols.

Entry	Esters	Triol and diols	Product <sup>a</sup>	Time (min)	Isolated yield (%) <sup>b</sup>
1		но-< <sup>ОН</sup>	О О ОН	5	75
2	Moo	но-{ <sup>ОН</sup> ОН	МеО ОН	5	73
3		но-{ <sup>ОН</sup> ОН	20N OH OH	4	78
4		но-{ <sup>ОН</sup>	ОН	4	75
5		но-{ <sup>ОН</sup> Он	ООНОН	4	80

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Table 1. Continued

Entry	Esters	Triol and diols	Product <sup>a</sup>	Time (min)	Isolated yield (%) <sup>b</sup>
6	<u> </u>	но-< <sup>ОН</sup>	Состон	6	63
7	i i ok	но-<Он	ОН	7	65
8	$\frac{1}{\sqrt{2}}$	HO	ООН	10	89
9		HO~~OH	ООООН	8	92
10	Å Å	HO~~OH	ООООН	12	85
11	i i k	HO	ООО	14	82
12		H0~0~0H	O O O OH	9	90

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<sup>&</sup>lt;sup>*a*</sup>All the products were characterized by <sup>1</sup>H, <sup>13</sup>C-NMR, and mass spectrometry. <sup>*b*</sup>Isolated yield (after column chromatography).

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To ascertain the role of the keto group in this reaction, ethyl butanoate was used as the ester instead of the  $\beta$ -keto ester. No transesterified product was seen in this case. Aryl saturated and unsaturated esters viz. ethyl cinnamate and ethyl hydrocinnamate did not give the transesterified product with glycerol (P-4; 4 min). The reactions did not work even on increasing the reaction time to 10 min. These observations indicate that transesterification of  $\beta$ -ketoesters with glycerol is due to the  $\beta$ -keto functionality. The importance of the position of the keto group in the ester for this selective acylation of glycerol was determined by using 2- (or  $\alpha$ -) oxo-4-phenylbutyric acid ethyl ester as a substrate for transesterification under the previously mentioned reaction conditions. No transesterified product was seen even after 10 min, suggesting that the keto functionality at  $\beta$  position is essential for this transesterification. This could be because only  $\beta$ -hydroxy esters have the possibility of forming an internal hydrogen bond between the -OH (enol form) and C=O, giving a six-membered ring facilitating the transesterification reaction.<sup>[23]</sup> A plausible explanation for the rapid transesterification in the reactions reported in this work could be the evaporation of the alcohols (viz. methanol, ethanol, iso-propanol, and tert-butanol) formed in the reaction because of the high final temperature  $(100-130 \,^{\circ}\text{C})$ , thereby shifting the equilibrium in the forward direction.

In conclusion, we have demonstrated that  $\beta$ -ketoesters undergo selective transesterification with polyols under solvent- and catalyst-free conditions with microwave irradiation.

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