γ-NITROKETONES AS KEY INTERMEDIATES FOR THE SYNTHESIS OF γ-DIKETONES

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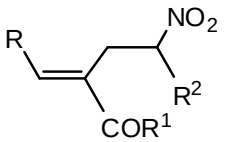
ABSTRACT: New α-methylene-γ-nitroketones **5** were synthesized, in fair to good yields, from the coupling reaction of a new family of allyl acetates **3** and nitroalkane salts.

Key words: Functional allyl acetates; nitroalkanes; addition-elimination reaction; α-methylene-γ-nitroketones.

INTRODUCTION

α-Alkylidene-γ-nitroketones **1** are valuable intermediates in organic synthesis as they are transformed into numerous fine chemicals and target molecules [1]. As a matter of fact, the nitro group can be easily transformed into other useful functional groups such as amines, aldehydes, or ketones moieties *via* nucleophilic addition reaction [2], reduction reaction [3] and other conversions [4-5]. Extensive studies have been devoted to the synthesis of this class of compounds. Over the last few years, they have been commonly prepared by the addition-elimination protocol from the Baylis-Hillman acetates and nitroalkanes using sodium hydroxide [6] or potassium carbonate [7] as bases. Although numerous studies have been reported on this topic, there is still a lack of general methods which covered the different types of nitro molecules **1**. To the best of our knowledge [8-10], functionalized nitro compounds **1** (R= H and R^1= alkyl or aryl) have not been reported in the literature. These limitations prompted us to develop a new simple synthesis of uncommon α-methylene-γ-nitroketones **5** which complete the existing routes for the synthesis of α-functional alkyl-vinyl ones **1** (Scheme 1).



1 : R= R^2= alkyl, aryl ; R^1= Me, Et.
5 : R= H; R^1=R^2= alkyl, aryl

Scheme 1

RESULTS AND DISCUSSION

We have recently published a concise method [11] for the synthesis of unprecedented α-hydroxymethyl alkyl (aryl) vinyl ketones **2** from an easy coupling reaction of aliphatic and aromatic 2,4-dioxoalkanoates and a large excess of aqueous formaldehyde (30%) using aqueous potassium carbonate solution (6-10M) as a base. We have demonstrated that the condensation of formaldehyde with 2,4-dioxoesters, at room temperature in the absence of organic solvents, gave

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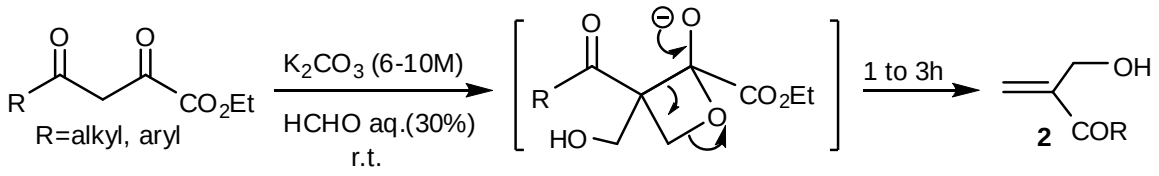
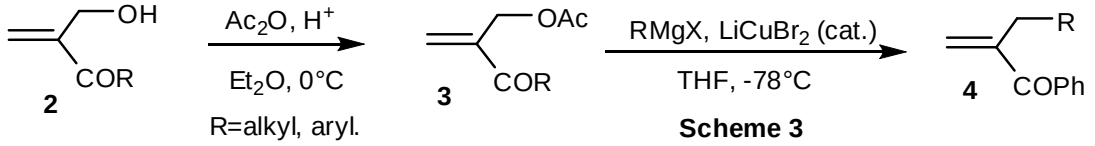
α-methylene-β-hydroxyalkanones **2** through the well established *tandem* hydroxymethylation-cyclization-elimination process (Scheme 2).



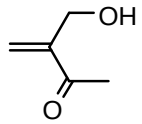
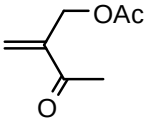
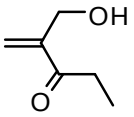
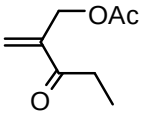
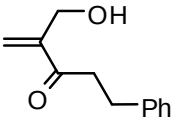
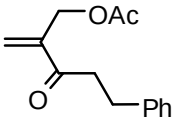
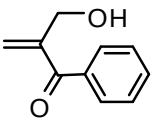
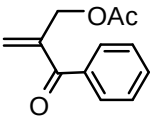
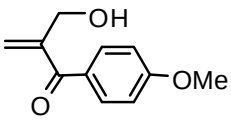
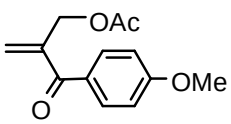
Scheme 2

Furthermore, we have proved that the conjugate addition of dialkyl organocuprates, generated in *situ* at low temperature from Grignard reagents [11,12] in the presence of a catalytic amount of $LiCuBr_2$ to the allyl acetate **3d**, led to the corresponding α-alkyl-vinyl ketones **4** through an addition-elimination or a nucleophilic S_N2' reaction. Our initial investigation on the nucleophilic reaction between allyl acetate **3d** and organocuprates prompted us to examine the electrophilic reactivity of some α-acetoxymethyl alkyl (aryl) vinyl ketones **3** for other useful transformations [13-17]. In continuation of our previous studies, we aim at preparing a new class of allyl acetates derivatives **3** in good yields through the acetylation of the corresponding alcohols **2** using acetic anhydride [18,19] in the presence of one drop of concentrated sulfuric acid (Scheme 3, Table 1).



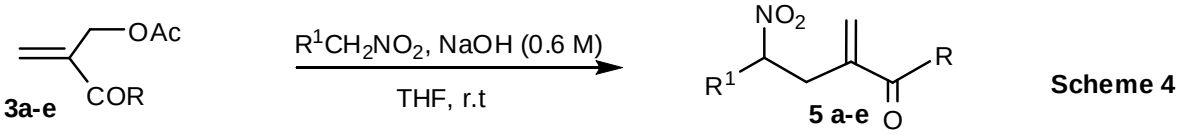
Scheme 3

Table 1: α-(Acetoxymethyl) vinyl ketones 3 from primary Baylis-Hillman alcohols 2

Alcohol **2**	Yield (%)*	Allyl acetate **3**	Time (h)	Yield (%)*
2a 	86	**3a** 	3	75
2b 	82	**3b** 	4	79
2c 	81	**3c** 	4.5	71
2d 	52	**3d** 	5	76
2e 	56	**3e** 	5	71

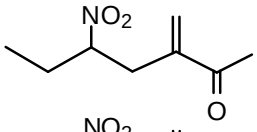
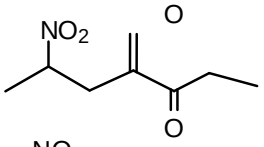
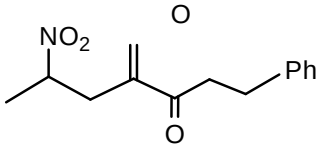
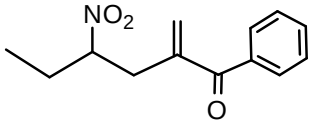
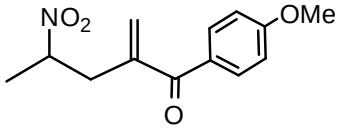
(*) Yields refered to the pure isolated products characterized by ^1H, ^{13}C NMR.

It has been reported that the Michael reaction of nitroalkanes with α,β-unsaturated carbonyl compounds could be carried out either, in homogenous solutions of the reactants in organic solvents [20] or in the presence of weakly basic resins as heterogeneous catalysts [21]. In order to provide an easy access to the uncommon α-methylene-γ-nitroketones **5**, from the known carbon-carbon bond forming reactions [22,23], it seemed plausible to proceed by the coupling reaction of allyl acetates **3** and some nitroalkanes [24] in aqueous basic medium (NaOH, 0.6 M) in the presence of tetrahydrofuran at room temperature (Scheme 4, Table 2). To optimize our method, various bases including NaH, RONa, NaOH or KOH have been used in various solvents but the reaction was not reproducible and only low yields of **5** were obtained.



Scheme 4

Table 2: α-Methylene-γ-nitroketones 5 from primary Baylis-Hillman acetates 3

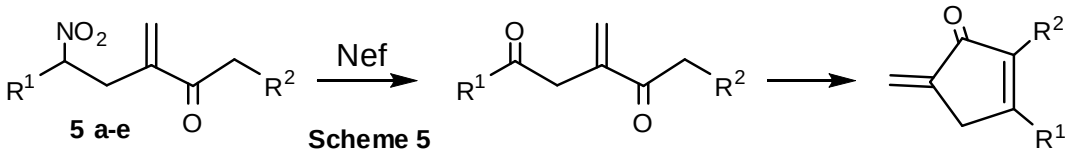
Allyl acetate **3**	$R^1CH_2NO_2$ (equiv.)	γ-Nitroketone **5**	Time (h)	Yield (%)*
3a	2	**5a** 	3	71
3b	2	**5b** 	5	73
3c	2.2	**5c** 	7	75
3d	3	**5d** 	24	81
3e	3	**5e** 	30	76

(*) Yields refered to the pure isolated products characterized by ^1H, ^{13}C NMR

CONCLUSION

We have developed a simple and efficient access to the uncommon functionalized nitro compounds **5**, which cannot be accessed *via* the conventional Morita-Baylis-Hillman (MBH) reaction of olefin and nitro compounds. We have also demonstrated that the new primary allyl acetates (four-carbon unit) **3,** obtained by the acetylation of primary alcohols **1** in acidic mild**,** can be easily displaced by nitroanions species, at room temperature using NaOH as a base, to provide the corresponding α-methylene-γ-nitroketones **5**. Moreover, the functionalized nitro compounds **5** could be converted *via* the Nef reaction into the corresponding γ-diketones used in the total synthesis of some cyclopentenones such as methylenomycin B ($R^1 = R^2 = Me$) [25,26], a powerful

antibiotic against both gram-positive and gram-negative bacteria [27]. This work will be the subject of our next report (Scheme 5).



Scheme 5

EXPERIMENTAL

All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F_{254}). For column chromatography, Fluka Kieselgel 70-230 mesh was used. ^{1}H and ^{13}C NMR spectra (fully decoupled) were recorded on a Bruker AMX 300 in $CDCl_3$ as a solvent and TMS as the internal standard.

General procedure for the synthesis of α-acetoxymethyl alkyl and aryl vinyl ketones 3

To a mixture of alcohol **2** (4 mmol), acetic anhydride (12-17 mmol) and 25 mL of anhydrous ether cooled at 0°C with an ice-bath, was added a drop of sulfuric acid. The reaction mixture was stirred at 0 ° C for one hour, then left to stir at room temperature. After completion of the reaction, the mixture was hydrolyzed with ice water and extracted with ether (3 x 20 mL). The organic layer is washed successively with sodium hydroxide solution (1.5 M) and brine until neutral pH, then dried over $MgSO_4$ and concentrated to dryness. The crude product obtained was purified on silica gel (AcOEt / Hexane, 1:9).

2-Methylene-3-oxobutyl acetate 3a. Yield (0.42 g, 75%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.14 (1H, s); 6.04 (1H, s); 4.83 (2H, s); 2.37 (3H, s); 2.10 (3H, s); ^{13}C-NMR (75MHz, $CDCl_3$): 200.3; 170.4;147.3; 126.0; 63.2; 25.9; 20.8.

2-Methylene-3-oxopentyl acetate 3b. Yield (0.49, 79%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.19 (1H, s); 5.96 (1H, s); 4.81 (2H, s); 2.7 (2H,q, *J*= 7.3 Hz); 2.09 (3H,s); 1.11 (3H, t, *J* = 7.3 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 201.5; 170.3; 142.6; 125.2; 62.1; 30.8; 20.7; 7.8.

2-Methylene-3-oxo-5-phenylpentyl acetate 3c. Yield (0.65g, 71%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29-7.17 (5H, m); 6.10 (1H, s); 6.00 (1H, s); 4.88 (2H, s); 3.04 (2H, t, *J*= 7.5 Hz); 2.91 (2H, t, J= 7.5 Hz); 2.07 (3H, s); ^{13}C-NMR (75MHz, $CDCl_3$): 201.4; 170.5; 146.7; 140.8; 128.9; 128.6;128.4; 126.2; 125.1; 62.4; 39.7; 22.8; 20.6.

2-Benzoylallyl acetate 3d. Yield (0.62, 76%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.85 (d, 2H, *J*= 7.5 Hz); 7.65 (t, 1H, *J*= 7.3 Hz); 7.40 (t, 2H, *J*= 7.5 Hz), 6.15 (s, 1H); 5.84 (s, 1H); 4.98 (s, 2H); 2.31 (s, 3H); ^{13}C-NMR (75MHz, $CDCl_3$): 195.9; 170.5; 142.4; 137.1; 136.6; 129.3; 128.3; 127.6; 63.2; 20.8.

2-(4-methoxybenzoyl) allyl acetate 3e. Yield (0.66, 71%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83 (2H, d, ^{2}*J*= 8.1 Hz); 6.94 (2H, d, ^{2}*J*= 8.1 Hz); 6.08 (1H, s); 5.79 (1H, s); 4.92 (2H, s); 3.88 (3H, s); 2.33 (3H, s); ^{13}C-NMR (75MHz, $CDCl_3$): 196.8; 170.6; 163.2; 146.2; 131.9; 129.7; 125.3; 113.6; 63.6; 55.5; 20.6.

General procedure for the synthesis of 2-methylene-4-nitro Ketones 5

To a mixture of the allyl acetate **3** (2 mmol) and the appropriate nitroalkane table **1** in THF (10mL) was added a solution of NaOH (3 mmol, 0.6 M). After the addition was complete, the mixture was stirred at room temperature for the time indicated in Table 1. The mixture was diluted with H_2O and extracted with ether (3x15mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed to give oil which was purified by column chromatography on silica gel (AcOEt/hexane, 1:9).

3-Methylene-5-nitroheptan-2-one 5a. Yield (0.24 g, 71%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.09 (1H, s); 5.88 (1H, s); 4.67 (1H, m); 2.75 (2H, dd, ^{2}*J*= 14.1 Hz, ^{3}*J* = 4.1 Hz); 2.33 (3H, s); 1.82 (2H, m); 0.92 (3H, t, *J*= 7.3 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 201.1; 141.2; 127.5; 85.5; 30.7; 24.4; 20.2; 9.8.

4-Methylene-6-nitroheptan-3-one 5b. Yield (0.24 g, 73%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.02 (1H, s), 5.77 (1H, s), 4.70 (1H, m); 2.75 (2H, dd, ^{2}*J*= 14.3 Hz, ^{3}*J*= 4.4 Hz); 2.62 (2H, q, *J*= 7.3 Hz); 1.48 (3H, d, *J*= 7.3 Hz); 1.06 (3H, t, *J*= 7.3 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 201.5; 142.7, 127.8; 82.6; 37.3; 30.5; 19.2; 8.2.

4-Methylene-6-nitro-1-phenylheptan-3-one 5c. Yield (0.37 g, 75%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29-7.17 (5H, m); 5.98 (1H, s); 5.68 (1H, s); 4.70 (1H, m); 3.01 (2H, t, *J*= 7.5 Hz); 2.90 (2H, t, *J*= 7.5 Hz); 2.76 (2H, dd, ^{2}J= 14.1 Hz, ^{3}J= 4.2 Hz); 1.45 (3H, d, *J*= 7.3 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 201.4; 146.7; 140.8; 128.9; 128.6;128.4; 126.2; 125.1; 82.3; 39.7; 22.8; 18.9; 8.7.

2-Methylene-4-nitro-1-phenylhexan-1-one 5d. Yield (0.37 g, 81%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (2H, d, *J*= 7.5 Hz); 7.54 (1H, t, *J*= 7.3 Hz); 7.45 (2H, t, *J*= 7.35 Hz); 5.97 (1H, s); 5.74 (1H, s); 4.66 (m, 1H); 3.17 (dd, 1H, ^{2}J= 14.3 Hz, ^{3}J= 2.6 Hz); 2.85 (dd, 1H , ^{2}J=14.3 Hz, ^{3}J= 10.6 Hz); 2.1 (m, 1H); 1.85 (m, 1H); 1.08 (t, 3H, *J*= 7.35 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 197.2; 142.1; 137.2; 132.2; 130.6; 128.7; 128.3; 89.2; 36.6; 27.1; 10.0.

1-(4-Methoxyphenyl)-2-methylene-4-nitropentan-1-one 5e. Yield (0.38, 76%) as a yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 7.82 (2H, d, ^{2}J= 8.1 Hz); 6.93 (2H, d, ^{2}J= 8.1 Hz); 6.02 (1H, s); 5.75 (1H, s); 4.70 (1H, m); 3.88 (3H, s); 2.75 (2H, dd, ^{2}J= 14.3 Hz, ^{3}J= 4.4 Hz); 1.48 (3H, d, *J*= 7.3 Hz); ^{13}C-NMR (75MHz, $CDCl_3$): 196.1; 163.0; 145.8; 131.7; 129.6; 125.0; 113.2; 89.1; 55.2; 35.8; 9.8.

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