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A MODIFICATION OF THE KNORR OXIDATIVE COUPLING METHOD FOR PREPARATION OF 1,4-DIKETONES

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Abstract: The oxidative coupling of β-keto esters has been achieved in good yield using NaOEt / I_2.

A variety of synthetic methods for the preparation of 1,4-diketones have been developed, [1-4] since 1,4-diketones are versatile intermediates for synthesis of some natural products consisting of cyclopentanone and furan ring system.

One of the representative and attractive routes to 1,4-diketones involves the oxidative coupling of β-keto esters by Na / I_2. This method, based on the early work of Knorr [5], has been used in synthesis of a number of lignans, a class of natural products with broad range of biological activities. [6-8] However, the reaction between sodium metal and β-keto esters in ether is slow and the reaction time is very long (for

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days) especially for large scale reactions. When more expensive sodium hydride is used instead of sodium metal, a large amounts of solvent (ether) is required.

The another method has also been reported for oxidative dimerization of β–keto esters using Ag_2O in dimethyl sulfoxide (DMSO) .However the dimer products are tetracarbethoxylene [9] , and it is not easy to separate the reaction products from the DMSO solution.

Recently, we found that β–keto esters could be conveniently coverted to 1,4–diketons in good yields.

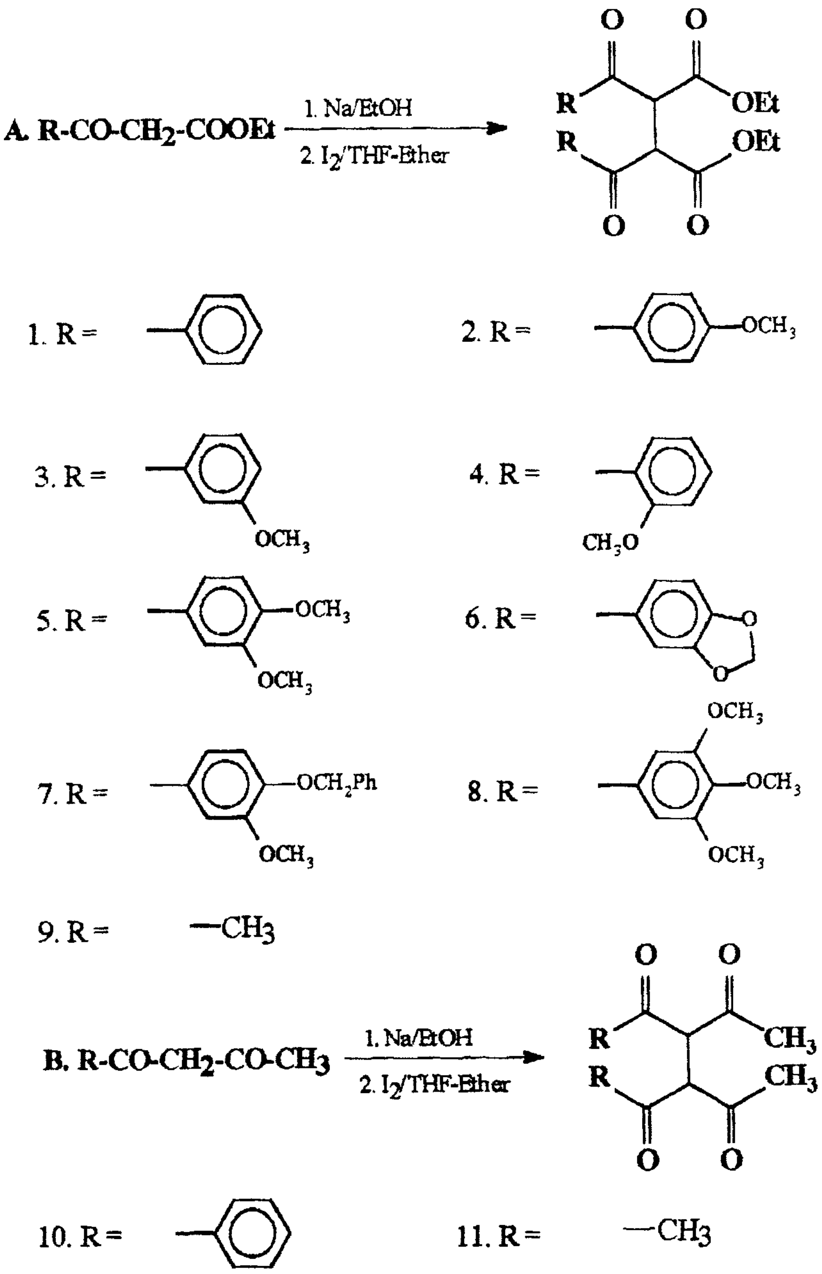
It is well known that the sodium salt of β–keto esters could be easily formed through the reaction of sodium metal and β–keto esters in absolute ethanol as the acidity of a β–keto ester (Pka = 11) is larger than that of ethanol (Pka = 18) [10] :

$$CH_3CH_2ONa + RCOCH_2COOEt \longrightarrow (RCOCHCOOEt)^- Na^+ + CH_3CH_2OH$$

However, the experiment on the oxidative coupling of sodium enolates of β–keto esters by I_2 in absolute ethanol failed. And the solubility of I_2 in alcohol is poor. Nevertheless we found that the oxidative coupling of sodium enolates of β–keto esters by I_2 in dry ether–THF mixture solution could be achieved smoothly and I_2 solid has excellent solubility in THF.

Hence, now we have developed an improved method for the oxidative coupling of β–keto esters. The general procedure is as follows (scheme 1):

After sodium metal (0. 1mol) was dissolved in absolute ethanol (50ml), an equal amount of β–keto ester was added at room temperature and the mixture was stirred in homogeneous state for 1 hr. The corresponding sodium salt of β–keto esters, obtained conveniently by removing solvent under reduced pressure at room temperature, was suspended in dry ether (150ml) and a solution of equal amount of iodine in dry THF (50ml) was added dropwise with vigorous stirring. The dimerized products of β–keto


A. R-CO-CH2-COOEt
1. Na/EtOH
2. I2/THF-Ether
O
O
R
OEt
R
OEt
O
O
1. R =
2. R =
OCH3
3. R =
OCH3
4. R =
CH3O
5. R =
OCH3
OCH3
6. R =
O
O
7. R =
OCH2Ph
OCH3
8. R =
OCH3
OCH3
OCH3
9. R =
CH3
B. R-CO-CH2-CO-CH3
1. Na/EtOH
2. I2/THF-Ether
O
O
R
CH3
R
CH3
O
O
10. R =
11. R =
CH3

Scheme 1

Table 1. Na–EtOH–I_2 system for the oxidative coupling of *β*–keto esters

Entry	Substrates	Coupling Products	Yield (%)	MS(m / z)	^{1}HNMR($CDCl_3$,δppm)
1	$R_1CO\ CH_2COOEt$	$R_1CO\ CH\ COOEt$ $R_1CO\ CH\ COOEt$	99	382(M^+,7),377(21) 364(15),291(64), 105(100).	7.3–8.3(m,10H),5.56(s,2H),4.00(q,J=7.Hz,4H),1.01(t,J=7Hz,6H).
2	$R_2CO\ CH_2COOEt$	$R_2CO\ CH\ COOEt$ $R_2CO\ CH\ COOEt$	95	442(M^+,20),424(10) 397(15),351(50), 290(62),135(100).	6.9–8.2(m,8H),5.50(s,2H),3.90(s,6H),4.17(q,J=7Hz,4H),1.23(t,J=7Hz,6H)
3	$R_3CO\ CH_2COOEt$	$R_3CO\ CH\ COOEt$ $R_3CO\ CH\ COOEt$	98	442(M^+,22),424(5) 397(3),350(28) ,290(45),135(100).	6.8–7.7(m,8H),5.40(d,J=5Hz,2H),3.90(s,6H)4.00(q,J=7Hz,4H),1.10(t,J=7Hz,6H)
4	$R_4CO\ CH_2COOEt$	$R_4CO\ CH\ COOEt$ $R_4CO\ CH\ COOEt$	96	442(M^+,13),440(14) 424(47),395(32), 292(61),135(100).	6.8–8.0(m,8H),5.33(s,2H),4.00(s,6H),4.21(q,J=7Hz,4H),1.33(t,J=7Hz,6H)
5	$R_5CO\ CH_2COOEt$	$R_5CO\ CH\ COOEt$ $R_5CO\ CH\ COOEt$	100	502(M^+,13),484(4) 411(5),165(100).	6.8–8.0(m,6H),5.51(s,2H)3.95(q,J=7Hz,4H),3.90(s,12H),0.99(t,J=7Hz,6H)
6	$R_6CO\ CH_2COOEt$	$R_6CO\ CH\ COOEt$ $R_6CO\ CH\ COOEt$	98	470(M^+,16),452(6) 425(3),149(100).	6.7–7.8(m,6H),6.0(s,4H)5.43(s,2H),4.00(q,J=7Hz,4H),1.10(t,J=7Hz,6H)
7	$R_7CO\ CH_2COOEt$	$R_7CO\ CH\ COOEt$ $R_7CO\ CH\ COOEt$	90[a]	654(M^+,53),609(13) 608(12),563(19). 91(100).	6.7–7.9(m,16H),5.47(s,2H),5.20(s,4H),3.93(m,10H),1.07(t,J=7Hz,6H)
8	$R_8CO\ CH_2COOEt$	$R_8CO\ CH\ COOEt$ $R_8CO\ CH\ COOEt$	92[a]	563(M+1,7),562 (M^+,23),544(3), 471(4),367(4), 321(9),195(100).	7.37(s,4H),5.50(s,2H),4.09(m,4H),3.93(s,18H),1.13(t,J=7Hz,6H)
9	$R_9CO\ CH_2COOEt$	$R_9CO\ CH\ COOEt$ $R_9CO\ CH\ COOEt$	75[a]	258(M^+,3), 256(M–2,6), 215(31),213(100)	4.47(s,2H),4.16(q,J=7Hz,4H), 2.40(s,6H),1.27(t,J=7Hz,6H)
10	$R_{10}CO\ CH_2CO\ CH_3$	$R_{10}CO\ CH\ COCH_3$ $R_{10}CO\ CH\ COCH_3$	34[a]	322(M^+,2),303(100) 280(61),262(36)	7.3–8.2(m,10H),5.90(s,2H),2.17(s,6H)
11	$R_{11}CO\ CH_2CO\ CH_3$	$R_{11}CO\ CH\ COCH_3$ $R_{11}CO\ CH\ COCH_3$	0[a]		

a.Isolated yield.

esters were obtained by simple filtration and distillation in almost quantitative yield, usually no purification is required.

The results are summarized in Table 1.

As shown in Table 1, the β–keto esters having an aryl group were readily dimerized with Na–EtOH–I_2 in excellent yields.However, under the same conditions, the corresponding dimer products of β–diketones were obtained in lower yields and no dimer of acetylacetone was isolated from the reaction mixture of oxidative coupling.Since the acidity of acetylacetone (Pka = 9) is the strongest among these compounds, its sodium enolate could be easier to form in alcoholic medium with NaOEt.So we think that the sodium enolate of acetylacetone is probably too stable to react with iodine.

Mechanistic studies and application of the present oxidative coupling method for the total synthesis of lignans are now in progress.

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