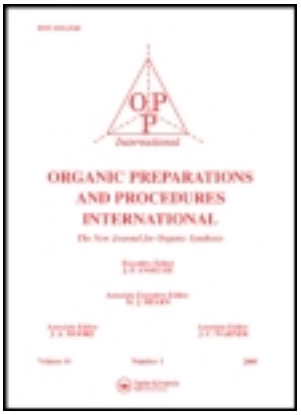

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Facile Carbethoxylation and Carbamoylation of Ketones

Pavel Pazdera [a] & Jan Simbera [a]

[a] Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry, Kotlarska 2, Brno, Czech Republic

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Facile Carbethoxylation and Carbamoylation of Ketones

Pavel Pazdera and Jan Simbera

Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry, Kotlarska 2, Brno, Czech Republic

α-Carbalkoxy and α-carboxamido derivatives of ketones are important compounds for the pharmaceutical and fine chemical fields and have been prepared by the carbalkoxylation and carbamoylation of enamines or of enolate ions generated by treatment of ketones with strong base such as LDA, sodium, potassium, lithium hydrides, Grignard reagents etc,[1–4] followed by alkoxycarbonylation with dialkyl oxalates[5,6] or carbonates[7] typicaly in benzene or tetrahydrofuran at low temperatures and under inert atmosphere.[2,3,8] There is still a compelling need to develop novel methods which would lead to higher yields of functional derivatives of 2-oxocarboxylic in shorter times and under milder conditions with simple work-up procedures.

The sonochemical phase-transfer-catalysis (PTC) under solid-liquid (S-L PTC) and liquid-liquid conditions (L-L PTC) is a very important and effective method to accomplish such purpose. Moreover L-L PTC is generally known to be very useful for the deprotonation of different H-X systems.[9] Synergism between PTC and ultrasound is also known.[10] Ultrasound irradiation has been shown to be a clean and valuable approach in organic synthesis over the last three decades and more convenient in comparison with the traditional methods.[1–8]

For these reasons, it was assumed that the generation of enolate anions from ketones by the synergic effect of ultrasound and S-L PTC should be comparable with the action of strong bases. A further advantage of S-L PTC over L-L PTC reactions is the fact that the use of highly concentrated aqueous alkaline hydroxide solutions (ca. 40%) that can lead also to competitive condensation reactions of the ketones, is avoided.

We performed the acylation of cyclic ketones **1** with variable ring size and on the acyclic ketones **3** with ethyl chloroformate and the results show that this method may be used for variety of ketones (*Scheme 1*). It is also evident that increasing alkylation at the α-carbon decreases the acidity of remaining α-hydrogen and the tendency toward enolization

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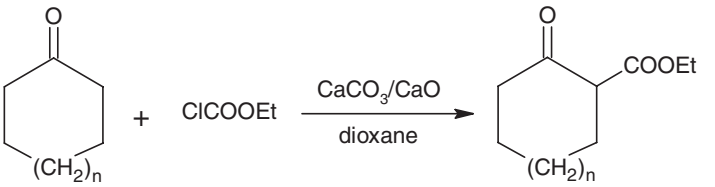
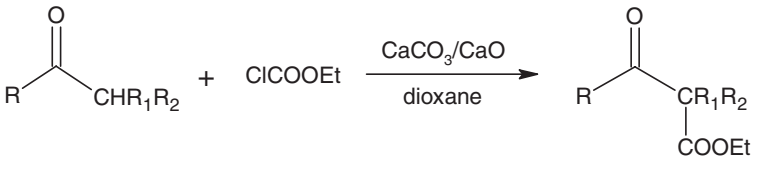
Address correspondence to Pavel Pazdera, Centre for Syntheses at Sustainable Conditions and their Management, Masaryk University, Faculty of Science, Department of Chemistry, Kotlarska 2, CZ-61137 Brno, Czech Republic. E-mail: pazdera@chemi.muni.cz



1 **2**

a) n = 0 b) n = 1 c) n = 2 d) racemic camphor



3 **4**

a) R = Me_3C, R_1, R_2 = H b) R = Me_2CH, R_1, R_2 = H c) R = Me_2CH, R_1,R_2 = Me

Scheme 1

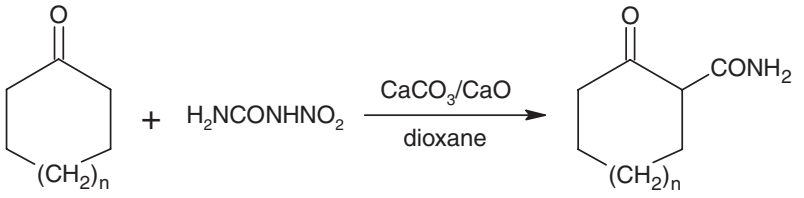
decreases as well. If two alternative groups can be deprotonated, the higher acidity of C-H moiety controls the regioselectivity of the reaction.

Similarly nitrourea has been utilized for the preparation of unsymmetrically substituted ureas by reaction with sufficiently basic amines,[11] its use for the carbamoylation of C-nucleophiles, namely ketones has not been studied till now (*Scheme 2*).

Of the various inorganic bases used, an equimolar mixture of $CaCO_3$/CaO proved to be the most effective combination. Dioxane (ultrasonic velocity U = 1360.0 m/s, 2 MHz, 25°C),[24] instead of toluene or other aprotic solvents, led to significantly shorter reaction times.

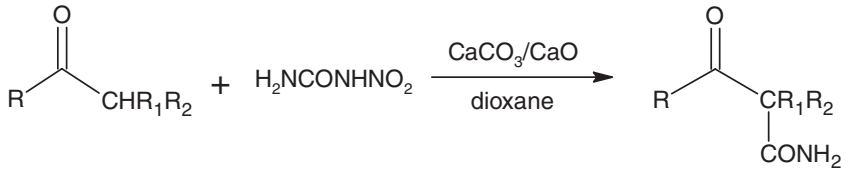
We observed that the reactions do not occur without PTC (5 mol% cetyltrimethylammonium chloride) and ultrasound (US). When PTC or US were used separately, the reaction rates increased only slightly; however, when both techniques (PTC and US) are applied simultaneously, strong synergic effect on the reaction rates was observed in the case of both types of reaction.

In conclusion we have developed a new and convenient method for the α-acylation of ketones in very good yields by reaction with ethyl chloroformate or nitrourea in the presence of non-hazardous inorganic bases in an aprotic solvent using simultaneous ultrasound irradiation. We have achieved very good yields in the formation of 2-oxo-carboxamides, which are only difficult to prepare by other methods. Reactions are performed under ambient temperatures and pressures and without using inert gas atmosphere. Moreover inorganic waste formed can then be separated by filtration and may be used further, even as a mixture (for example in building material industry).



1 **5**

a) n = 0 b) n = 1 c) n = 2 d) racemic camphor



3 **6**

a) R = Me_3C, R_1, R_2 = H b) R = Me_2CH, R_1, R_2 = H c) R = Me_2CH, R_1,R_2 = Me

Scheme 2

Experimental Section

The starting ketones were purchased from Sigma-Aldrich and used without purification. The progress of the reaction was monitored on a HPLC chromatograph Knauer Smartline Pump 1000, Manager 5000 and Alltech 3300 ELSD detector was used. For sonication, an Ultrasonic cleaner model D4a from Qteck-Germany was used, ultrasonic frequency 35 kHz, nominal power 240 W and volume of the vessel 3.5 l. The reaction temperature (25 ± 2°C) was controlled using an external incorporated thermoregulator in the water bath.

General Procedure for Synthesis of Compounds (2, 4, 5, 6, Table 1)

The corresponding ketones **1** or **3** (5 mmol), equimolar mixture of $CaCO_3$/CaO (1.56 g, 10 mmol) and cetyltrimethylammonium chloride (0.08 g, 5 mol%) and ethyl chloroformate (0.54 g, 5 mmol) or nitrourea (0.53 g, 5 mmol) were added into a one-neck round-bottom flask containing dioxane (5 ml). Then the reaction mixture was sonicated in an ultrasound bath for the times listed in *Table 1* and monitored by HPLC. The reaction temperature was set to 25°C. After completion, the mixture was filtered and the solid washed with dioxane (5 ml). The combined organic filtrates were evaporated *in vacuo*. The crude carbethoxylates were purified by distilation *in vacuo* and the corresponding carboxamides by crystalization, respectively.

Table 1
Carbethoxy and Carboxamido Derivatives **2, 4, 5, 6**

Product	Yield[a] (%)	Time (hrs)	bp. or mp. (solvent) (°C/mm Hg or °C) Found	*lit.*
2a	95	3	115–117/20	114–116/20[12]
2b	95	3	104–107/10	106–109/10[13]
2c	95	3	115–118/10	118–124°C/14[1,14]
2d	90	5	139–140/10	166°C/20[13]
4a	95	5	83–85/10	96–98/15[13]
4b	95	5	89–91/15	89–91/14[15,16]
4c	90	5	89–91/16	87–89/14[17]
5a	85	3	94–96 (ethanol)	96–97[18]
5b	95	3	134–135 (ethanol)	136–137[18]
5c	80	3	116–117 (ethanol)	118[19]
5d	80	5	114–116 (petrol ether)	116–117[20]
6a	95	5	82–84 (ethyl acetate)	83–84[21]
6b	95	3	45–47 (ether)	46–49[22]
6c	90	5	107–110 (ethanol)	110–111[23]

[a]Determined by HPLC.

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