

Tighter ion pair effect and scale-up study in microwave assisted aminolysis of enolizable esters using potassium *tert*-butoxide (*t*-BuOK)

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The tighter ion pair effect and scale-up study in aminolysis of enolizable esters using potassium *tert*-butoxide (*t*-BuOK) under microwave irradiations is described. This method provides synthetic advantages in terms of reaction time, product yields, eco-friendly environment and scale-up feasibility over the conventional heating method.

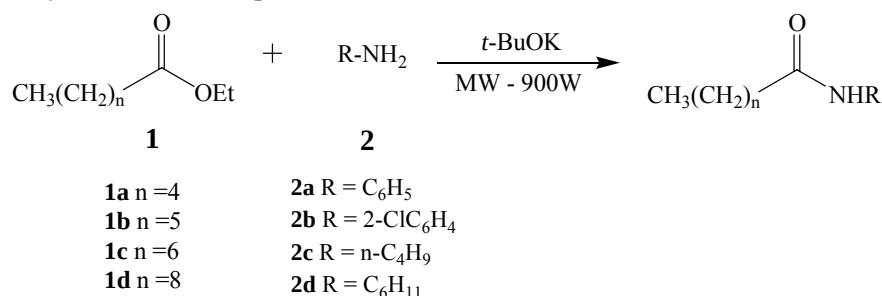
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The amide moiety is an important constituent of many biologically active compounds so the understanding of the formation, properties and reactions of amides is important to the future development in polypeptides and protein chemistry¹. Several methods are reported in the literature for the transformation of esters to amides²⁻⁸, but the practical applications of these methods have been limited for a number of reasons. The main reason is that these methods require harsh conditions such as high temperature and extended reaction time, which have been overcome by carrying the reactions under microwave irradiations. In recent years, microwave-assisted transformations have become popular in promoting organic reactions. Organic synthesis under microwave irradiations has significant advantages as compared to classical heating techniques⁹⁻¹¹. The major advantages of microwave heating are the instantaneous “in core” heating of materials, in an effective and selective manner, in contrast to conventional heating¹². Recently, a few reports have appeared on the microwave-assisted synthesis of simple amides¹³,

however none of these reports includes the effect of tighter ion pair on rate of reaction and product yield. Scale-up capability has also not been studied. In continuation of our work¹⁴ for the development of new synthetic methods, herein we report the study of tighter ion pair effect and scale-up feasibility in the direct aminolysis of enolizable esters by taking long chain esters in the presence of *t*-BuOK, which have not been studied earlier.

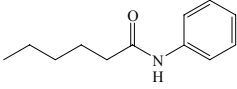
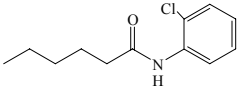
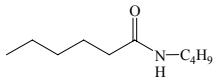
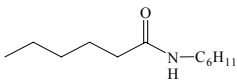
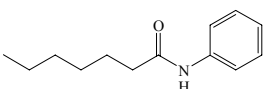
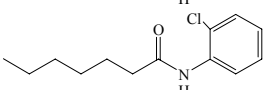
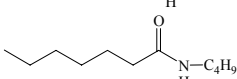
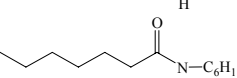
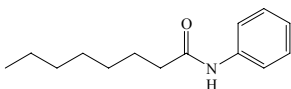
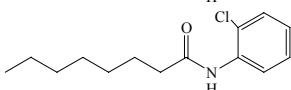
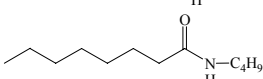
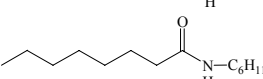
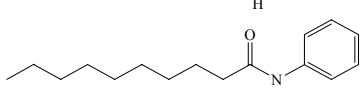
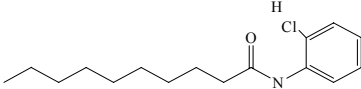
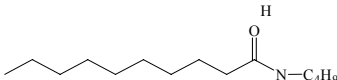
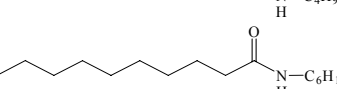
Results and Discussion

In our study long chain esters have been taken, this is essentially because in these esters α -hydrogen atom is not acidic and hence *t*-BuOK do not abstract α -hydrogen atom and results in excellent yield of the amides without any side products. It involves irradiation of premixed ester **1**, amine **2** and *t*-BuOK in equivalent mole ratio under microwaves at 900 W power level (**Scheme I**). The reaction time ranges from 2 to 5 min depending upon the structures of esters and amines.



Scheme I

Table I—Microwave assisted synthesis of amides from enolizable esters

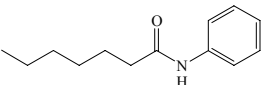
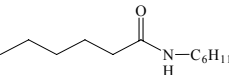
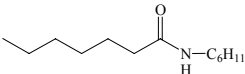
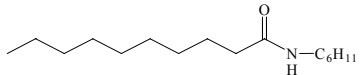
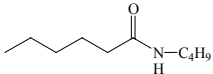
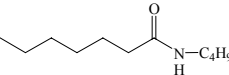
Entry	Ester	Amine	Amide	Reaction time (min) Power - 900W	Yield isolated (%)
1	1a	2a		2.25	94
2	1a	2b		4	88
3	1a	2c		3.5	91
4	1a	2d		5	98
5	1b	2a		4	93
6	1b	2b		5	84
7	1b	2c		6	90
8	1b	2d		4	95
9	1c	2a		3	95
10	1c	2b		5	84
11	1c	2c		7	92
12	1c	2d		3.5	96
13	1d	2a		2.5	92
14	1d	2b		5	90
15	1d	2c		8	93
16	1d	2d		4	96

The reaction that takes place is very clean, involves easy work-up and excellent yields as compared to the conventional heating. The results of a variety of substrates are summarized in **Table I**.

The reaction time and yields of the products under microwave were compared with the conventional

heating also. In conventional heating procedure, a reaction flask fitted with reflux condenser was charged with ester, amine and *t*-BuOK in equivalent mole ratio in DMSO as a solvent. The mixture was heated to 190°C and the reaction products were analyzed by GC-MS. In comparison with

Table II — Comparative study* of microwave heating and conventional heating

Entry	Amide	MW heating time (min.)	Yield (%)	Conventional heating Time (hr.)	Yield (%)
1		4	93	25	69
2		5	98	26	68
3		4	95	25	74
4		4	96	25	78
5		3.5	91	24	68
6		6	90	25	66

*Comparative study of microwave and conventional heating was carried out under optimized condition.

conventional heating protocol, microwave heating has advantages in terms of reaction time and product yield (Table II).

Effect of microwave power on the reaction time and product yield of N-phenyl hexamide

The large difference in yields ($MW \gg \Delta$) may be a consequence of the polar transition state interaction with electric field component of microwave radiations^{15,16}. In order to optimize the microwave power, the reaction mixture was exposed to the electromagnetic field at different power levels. This step allowed us to determine adequate conditions of incident power and irradiation time. The experiments were conducted at three different power levels to compare reaction time and product yield (Table III).

Effect of microwave irradiation time on the product yield of N-phenylhexamide at 900W, 450W and 100W

The effect of irradiation time on the yield of a product was also investigated. We found that yields were affected by time of microwave exposure. The maximum yield was obtained within 145 sec at 900W (Table IV).

Tighter ion pair effect

The plausible mechanism involves, a claisen type condensation involving a nucleophilic attack of an

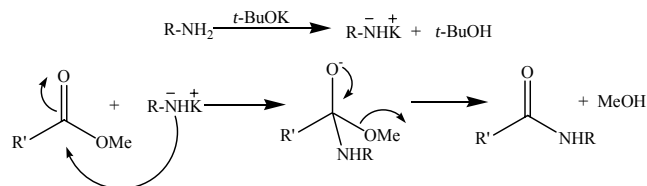
Table III — Effect of MW power on the reaction time and product yield of N-phenylhexamide

Entry	Microwave Power (W)	Reaction time	Yield (%)
1	100	25 min	66
2	450	4.75 min	82
3	900	2.25 min	94

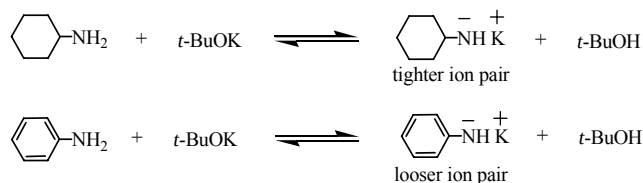
Table IV — Effect of MW irradiation time on the product yield of N-phenylhexamide

Entry	MW irradiation Time	Yield (%)
At 900W		
1	15 sec	48
2	45 sec	66
3	75 sec	73
4	105 sec	77
5	145 sec	94
At 450W		
1	15 sec	49
2	45 sec	53
3	105 sec	65
4	165 sec	70
5	225 sec	72
6	285 sec	82
At 100W		
1	1 min	42
2	3 min	51
3	9 min	55
4	16 min	62
5	25 min	66

anion (generated by abstracting a hydrogen atom from amine by a strong base) followed by loss of methoxide ion leading to formation of an amide.



The effect of amine structure on the microwave assisted conversion of ester to amide has been studied. The microwave specific effect depends on the nature of reactive species in connection with ionic dissociation.



As expected, we found that the transformations with tighter ion pair (cyclohexyl-NH⁻K⁺) exhibit the larger microwave effects and has higher yield of product (**Table I**). The aryl amines undergo reaction at slower rate compared to aliphatic amines, which is due to delocalization of the negative charge on amide anion, which in turn looses the association of ion pair (Ph-NH⁻K⁺). This suggests that, the microwave effects are clearly substituent dependent and optimal with tighter ion pair¹⁷.

Scale-up capability

The specific role of *t*-BuOK was also established by carrying out the reaction in the absence of base as well as in presence of KOH as a base. We found that, when the reaction was carried out in absence of *t*-BuOK, the conversion could not take place. Similarly, decomposition of reaction mixture was observed when KOH was used as a base. This indicates that *t*-BuOK is the suitable base for the conversion of enolizable esters to amide.

No doubt, microwave assisted transformations have become popular in promoting organic reactions. However, most of these transformations lack scale-up capability¹⁸. This constraint restricts the use of this technology for large-scale synthesis. We also studied the reproducibility and scale-up feasibility of the developed microwave protocol. To prove the concept, aminolysis of methyl hexanoate with cyclohexylamine was chosen. We found that N-cyclohexyl-

hexamide could be synthesized at 10 g scale with consistent yield and short microwave residency time. Since the reaction was carried out in domestic microwave oven (Samsung equipped with inverter technology that provides a better control of MW power to a desired level) further up-scalability could not be attempted. However, this should be possible by using advance microwave ovens.

Conclusion

The study explains the effect of tighter ion pair formation on the rate of reaction and product yield. The developed methodology can be scaled-up by using advance microwave oven. Thus, the present microwave protocol provides an efficient method for the aminolysis of long chain enolizable esters with quantitative yield, rapid reaction time and has scale-up capability.

Experimental Section

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. ¹H NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in δ, ppm) against TMS as internal standard; and IR spectra as KBr pellet on a Perkin-Elmer model BXII FTIR spectrophotometer (ν, cm⁻¹). The GC-MS analysis was performed on Varian 3400GC coupled to a TSQ 7000 mass spectrometer (Finnigan Mat.)

In a typical experimental procedure, the ester (0.01 mole) and amine (0.01 mole) was taken in a conical flask and potassium *tert*-butoxide (0.01 mole) was added to this premixed mixture. The reaction mixture was then exposed to microwave irradiations at 900 W for a specified time (**Table I**). The exposure should be intermittent with 15 sec break in order to avoid formation of hot spots. The reaction was monitored on TLC (silica plates, 10% acetone in chloroform) and GC. After completion of reaction, the reaction mixture was extracted with ethyl acetate. On evaporation of solvent a crude product was obtained, which on tritaring with petroleum ether gave pure amide.

The temperature of the reaction was measured by keeping the material in a glass container and then inserting the thermometer in the reaction mixture after reaction is over¹⁹ and the bulk temperature recorded is in the range of 120-30°C.

The spectral data of some representative products are given as follows:

N-Phenylhexamide (entry 1): IR (KBr): 3303, 3092, 2930, 1666, 1225, 755 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.85 (t, 3H, CH_3), 1.275-1.3125 (m, 4H, CH_2CH_2), 1.675 (m, 2H, CH_2), 2.3 (t, 2H, CH_2), 7.05-7.45 (m, 5H, Ar-H), 8.0 (s, 1H, NH); MS: m/z 191 (M^+ , 6%), 135 (9%), 120 (2%), 93 (100%), 77 (8%), 65 (9%).

N-Chlorophenylloctamide (entry 10): IR (KBr): 3284, 2923, 2850, 1661, 1528, 1440 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.96 (t, 3H, CH_3), 1.29-1.30 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.57 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 8.0 (s, 1H, NH), 6.94-7.58 (m, 5H, Ar-H); MS: m/z 281 (M^+ , 1%), 253 (14%), 218 (26%), 169 (18%), 127 (100%), 99 (14%), 57 (50%).

N-Cyclohexyloctamide (entry 12): IR (KBr): 3301, 2928, 2854, 1638, 1547 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.96 (t, 3H, CH_3), 1.29-1.30 (m, 8H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2$), 1.57 (m, 2H, CH_2), 2.18 (t, 2H, CH_2), 8.0 (s, 1H, NH), 1.44-1.60 (m, 10H, cyclohexyl ring-H), 3.54 (m, 1H, cyclohexyl ring-CH); MS: m/z 225 (M^+ , 6%), 196 (5%), 154 (20%), 144 (100%), 141 (73%), 126 (5%), 99 (9%), 56 (34%).

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