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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8281–8284

Highly efficient microwave-accelerated preparation of β-ketoimines

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Received 14 August 2007; revised 15 September 2007; accepted 25 September 2007

Abstract—We present here a new and efficient methodology for the β-ketoimine ligand with microwave heating system. The new method showed faster reaction rates, higher yields, and selectivities of the desired compounds in the absence of solvents.

The application of microwaves, as an efficient heating source for organic reactions,[1] was recognized in the mid 1980s. Over 3500 papers describing successful reactions with dramatically enhanced reaction rates have been published. High yields, clean reactions, employment of milder and less toxic reagents and solvents, and simple experimental procedures are known advantages of this heating technology and this methodology has been considered one of the most important tools in the green organic synthesis.[2] This technology has also been adopted successfully in the solid-phase organic synthesis (SPOS), regarded as one of the key tools for combinatorial chemistry for generating libraries of small organic molecules.[3]

Various polydentate ligands have been used to increase the stability of the complexes by anchoring the coordination sites and chelate effect. Among these polydentate ligands, β-diketonate ligands have drawn much interest due to their unique resonance stability and they have been investigated with virtually every metal and metalloid in the periodic table. These extensive works have been well reviewed in as early as late 70s.[4] Recent revived attention to this research field can be mostly attributed to the explosive development in the information industry. Very high integrated circuit and highly dense memory required in this field incited the development of new processes such as metalloorganic chemical vapor deposition (MOCVD) or atomic layer deposition (ALD). Many of the stable and volatile precursors suitable to these processes contain β-diketonate analogs. Modification of this type of ligands introduced various kinds of β-ketoiminate or β-diketiminate ligands and complexes of special groups including group 2 was extensively reviewed.[5] The advent of single-site catalysts with non-cyclopentadienyl (Cp) ligands for olefin polymerization has extended the application of these ligands. Asymmetric analogues have shown the potential for the asymmetric synthesis.

However, further application of these ligands, especially β-ketoiminates with bulky substituents has been deterred by low overall yields and long reaction time. It has been shown by Varma et al.[6,7] that condensation reactions between primary and secondary amines or sulfonylamines and aldehydes or ketones are substantially accelerated by microwaves under solvent-free conditions. Analogous condensation reactions with hydrazine[8] or carboxylic acids[9] have been reported to proceed with more enhanced efficiency on microwave heating. With help of domestic microwave oven, Hamelin et al. prepared some β-ketoimines from acetylacetone and high boiling amines,[10] and Braibante et al. also reported the synthesis of β-enamino carbonylic compounds from cyclic or acyclic, α-chloro-substituted β-dicarbonyl compounds and amines or ammonium acetates in the presence of K-10 montmorillonite with high yields.[11]

Keywords: Microwave-assisted synthesis; β-Ketoimine, β-diketone, amines, condensation reaction.
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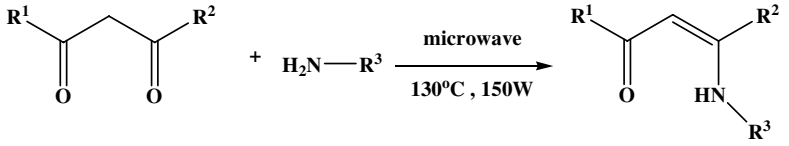
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.09.143

In connection of our previous efforts to prepare various derivatives of β-ketoiminates to the application of noble MOCVD precursors and polymerization catalysts,[12] we have tried to find a way to prepare these ligands, especially with bulky substituents, more efficiently. Herein we report that the preparation of β-ketoimines assisted by microwave heating can result in higher yields and shorter reaction times than conventional condensation reactions.

Typical preparative procedures are as follows: In a 10-mL glass tube were placed $CH_3C(O)CH_2C(O)CH_3$ (1.0 g, 10 mmol), (2-NH_2CH_2)Pyridine (1.10 g, 1.0 mmol), HCl (2–3 drop), and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity (CEM Co., Discover). When microwave was irradiated at a power of 150 W or 300 W, the temperature was raised from room temperature to 130 °C. Once the predetermined temperature was reached, the reaction mixture was held at that temperature for 5 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and then the yield and selectivity were confirmed by ^{1}H NMR (Varian Unity Inova 400 (400.265 MHz) or Varian Gemini 2000 (199.976 MHz)).

As shown in Table 1, microwave-assisted preparation proceeds much faster with high yield and selectivity irrespective of the natures of β-diketones or amines used. However, 1,3-diphenyl-1,3-propandione (runs 14–20),

Table 1. Comparison between microwave[a] and conventional synthetic methods (GM)[b]



Run	β-Diketone		Amine	GM	Microwave	
	R^1	R^2	R^3	Yield (%)	Yield (%)	Selectivity (%)
1	Me	Me	$(CH_2)_2OH$	90[13a]	88	100
2			$CH_2CH(Me)OH$	89[13a]	90	100
3			$C(Me)_2CH_2OH$	64[13b]	81	100
4			$(CH_2)_2OMe$	90[13c]	98	100
5			$(CH_2)_3OMe$	95[13c]	98	100
6			*o*-$CH_2(C_6H_4)OMe$	70[13c]	95	100
7			2-(CH_2)pyridine	66[13d]	96	100
8			2-$(CH_2)_2$pyridine	70[13d]	89	95
9			$CH(Me)CH_2OMe$	88[13d]	92	100
10			*p*-PhOMe	—	77	100
11			$CHMe_2$	—	93	100
12			CMe_3	—	87	100
13			$(CH_2)_2Me$	—	96	100
14	Ph	Ph	$(CH_2)_3OMe$	78[13c]	83	100
15			$CH_2CH(Me)OH$	—	81	100
16			$CH(Me)CH_2OMe$	30[13c]	78	100
17			2-(CH_2)pyridine	66[13d]	95	92
18			2-$(CH_2)_2$pyridine	34[13d]	85	90
19			*o*-$CH_2(C_6H_4)OMe$	51[13c]	91	100
20			2-Me-6-OMe–Ph	53[13c]	82	100
21	*t*-Bu	*t*-Bu	$(CH_2)_2OH$	—	60*	100
22			$CH_2CH(Me)OH$	3.6[13b]	68*	100
23			2-(CH_2)pyridine	—	65*	100
24			2-Pyridine	—	76*	100
25	*i*-Pr	*i*-Pr	$(CH_2)_2OH$	84[13b]	93	100
26			$CH_2CH(Me)OH$	85[13b]	93	100
27			$(CH_2)_2OMe$	82	97	100
28			$CH(Me)CH_2OMe$	81	87	100
29	CF_3	CF_3	$(CH_2)_3OMe$	41[13c]	76	95
30			2-(CH_2)pyridine	—	59	80
31	Ph	Me	$(CH_2)_2OH$	—	100	100
32			$CH_2CH(Me)OH$	—	92	100
33			2-(CH_2)pyridine	33[13c]	99	100
34	*t*-Bu	Me	$(CH_2)_2OH$	89[13b]	94	100
35			$CH_2CH(Me)OH$	78[13e]	91	100

[a] Molar ratio β-diketone (10 mmol), amine(11 mmol), reaction time: 5 min, temperature: 130 °C, microwave power: 150 W, no solvent, isolated yield. Selectivity: [β-ketoimine]/([β-ketoimine] + [β-diketimine])determined by ^{1}H NMR.

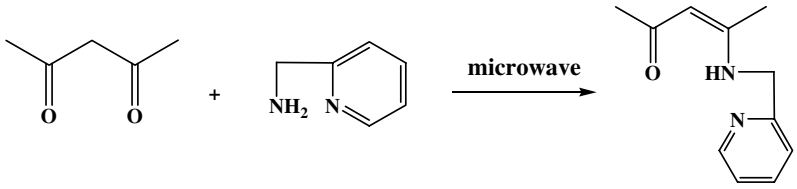
[b] General organic synthesis of several steps.

* Reaction time: 1 h, 10 equiv of pyridine.

2,6-tetramethyl-3,5-heptadione (TMHD) (runs 21–24), or hexafluoroacetylacetone (runs 29–30) showed lower yields than acetylacetone (runs 1–13). It appears that some electronic effects (generally, lower yields with electron withdrawing substituent on β-diketones) may work in the first two cases but steric effect may be the reason for the lower yield in the TMHD cases. Meanwhile, almost quantitative yields were obtained in the cases of 2,6-dimethyl-3,5-heptadione (runs 25–28) and the steric effect on the yield is doubtful. It is worth reminding that reaction time is 1 h in the TMHD reactions but it is only 5 min in other ones. For the steric effect by the substituents of amines, it is not easy to find the trends from the experimental results; with acetylacetone two methyl groups attached to the α-carbon of the hydroxyalkylamines reduced the yield (from 85% to 65%) significantly (runs 1 and 3) but for simple alkylamines, steric bulkiness induces erratic results (93%, 87%, 96% for *i*-Pr, *t*-Bu, *n*-Pr, respectively) (runs 11–13) or a minor change was induced for alkoxyalkylamines (runs 4 and 6). The effect by the substituent on β-carbon appears to be negligible (runs 1, 2 and 25, 26) but in some cases, significant effect was observed (runs 31 and 32). With 2,6-dimethyl-3,5-heptadione, one methyl group is enough to reduce the yield by 10% (runs 27 and 28), while with 1,3-diphenyl-1,3-propandione, the presence of one methyl shows less effect (runs 14 and 16). The effect of alkyl chain length also appears to be erratic. Moreover, dissymmetric β-diketones give β-ketoimines where amines are introduced to the side of less bulky substituent, Me (runs 31–35), which were confirmed by NOE experiments.

The reason for the lower yield except steric factor in the TMHD reactions cannot be proposed yet. However, as mentioned before, substitution of *t*-Bu with *i*-Pr in β-diketones greatly improve the yield and reaction time. Volatility of β-diketones may be another reason. Since the pressure reaction cell with a screw sealed lid was not employed, evaporation of β-diketones after absorption of microwave radiation may occur. Even though the boiling points of acetylacetone, 1,3-diphenyl-1,3-propandione, hexafluoroacetylacetone, TMHD, and 2,6-dimethyl-3,5-heptadione are quite different (140 °C, 219–221 °C (18 mmHg), 70–71 °C, 72–73 °C (6 mmHg) and 66 °C (8 mmHg), respectively), more volatile (or

Table 2. Preparation results with various experimental factors[a]



Run	Amine (equiv)	HCl	Power (W)	*T* (°C)	Time (min)	Yield (%)	Selectivity[b] (%)
1	1.0	No	60	130	5	74	100
2			100	130		82	100
3			150	60		22	100
4				80		35	100
5				100		48	100
6				130	1	36	100
7					2	68	100
8					5	92	98
9					10	91	93
10					20	78	90
11				150	5	94	99
12				200		86	90
13			200	130		91	99
14			300			84	90
15	1.1		150	130	5	96	100
16	1.2		60	130	5	78	100
17			100			88	99
18			150			98	100
19			200			95	100
20			300			91	95
21	1.0	Yes	150	60	5	43	100
22				80		80	100
23				100		95	100
24				130	1	74	100
25					2	88	100
26					5	99	100
27				150	5	97	100

[a] Molar ratio β-diketone (11 mmol = 1.1 equiv), amine (10 mmol = 1.0 equiv), HCl (0.2 mmol), isolated yield.

[b] Selectivity: [β-ketoimine]/([β-ketoimine] + [β-diketimine]) determined by ^{1}H NMR.HCl: 16 M aqueous solution.Conventional synthesis: EtOH, 80 °C, HCOOH, 24 h, isolated yield: 66%.

low bp) β-diketones still produce the product much higher yield in much less time. Volatility of β-diketones after absorption of microwave radiation may not be determined by their boiling point only. In the TMHD reactions, much more amines were left and significant amount of TMHD was solidified on the surface of watch glass, which is placed on top of the reaction flask and cooled by dry ice after irradiation for 1 h even though equal equivalents of reactants were used. In these cases, 10 equiv of pyridine or triethylamine are used to get significant amounts of corresponding β-ketoimines. The role of extra amines is not clear but formation of ammonium salts between amines and β-diketones may be expected and volatility can be reduced. Braibante et al. also used the same strategy to improve the yield of reaction employing low boiling amines.[11] He used ammonium acetates for amines to obtain β-ketoimines with improved yields. However, no peak assignable to this salt in the ^{1}H NMR spectrum of the product between TMHD and pyridine was observed.

In Table 2, effects of various reaction factors are summarized. The effect of reaction time on the yield was monitored and it was found that yield increased with the increase of reaction time up to 5 min but slowly decreased after that time (150 W, 130 °C). The yields also increased with the increase of microwave power until 150 W and decreased again with further increase of power but small differences in yields indicate that the effect of microwave power may be not significant. However, this effect depends on the amount of amines. When 1.0 equiv of amine is used, 150 W is the optimal power but 200 W is the optimal power with 1.2 equiv of amines. Generally addition of HCl (0.2 mmol, 16 M aqueous solution) enhanced the yields significantly in all the temperature ranges tested and the yield increased with the temperature but the effect of temperature above the optimal one (130 °C) is negative. Addition of more amines resulted in higher yield and slightly excess β-diketones have been used for the easy purification of the products.

In summary, various β-ketoimines were obtained in the absence of solvent but with the aid of microwave in much less reaction time with higher yields. It is found that this method can be applicable irrespective of the nature of β-diketones and amines.

Acknowledgments

Authors show their appreciation for the financial support of Samsung Electronics Co. (2005–2006) and T. Athar thanks for the Brain Pool Fellow (2006).

Supplementary data

Spectroscopic data for all new compounds prepared. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.143.

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