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Ultrasound-assisted synthesis of substituted guanidines using 1*H*-pyrazole-1-carboxamidine and *S*-methylisothiouronium sulfate under solvent-free conditions

Mitsue Fujita*, Yoshio Furusho

Department of Chemistry, Shiga University of Medical Science, Seta, Otsu, Shiga 520-2192, Japan

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ABSTRACT

We have investigated ultrasound-assisted synthesis of guanidine derivatives using 1*H*-Pyrazole-1-carboxamidine (PyzCA) and S-substituted isothiouronium sulfate (MeITU). The guanylations of several amines are promoted by ultrasound sonication under solvent-free conditions, and proceed under mild conditions. It is of particular interest that the guanylations do not require bases in most cases.

1. Introduction

Guanidine functionality is often found in a number of biologically and pharmaceutically relevant compounds, playing important roles in functions of those molecules [1–5]. A wide range of biological activities are attributed to the high basicity and ability to form strong hydrogen bonds under physiological conditions, including antibacterial, antifungal, antiviral, anti-inflammatory, and anti-tumor activities [4,5]. Furthermore, various guanidines have been employed as key building blocks for supramolecules, synthetic receptors, sensors as well as catalysts [6–12].

The demand for guanidine derivatives have thus been growing to date. Accordingly, various new synthetic methods have been developed for obtaining this class of compounds [13,14]. Among them, guanylation of amines is the most popular way to guanidine derivatives, since the starting materials are often readily available and relatively inexpensive [15–30]. Several kinds of guanylation reagents have been developed to date, including isothiouronium salts, carbodiimides, cyanamides, 1*H*-pyrazole-1-carboxamidine, *etc*. Nevertheless, these methods sometimes confront problems such as low yields and harsh conditions.

Sonochemical methods have recently proved a powerful technique for facilitating various chemical reactions [31–37]. Ultrasonic energy can cause the formation and adiabatic collapse of transient cavitation bubbles of gaseous substances [38]. Owing to this cavitation effect, solubility, diffusivity, penetration, and mass transportation and turbulent flow of chemical species are enhanced in certain reactions. Consequently, ultrasound in organic synthesis often shortens reaction times and reduces the formation of undesired side products, thereby enhancing product yield and selectivity and requiring in milder conditions than conventional methods. In addition, the ultrasound-assisted synthesis is applicable to solvent-free or low-solvent conditions [39–44]. Therefore, it is often called a green method with its high efficiency, economic performance, low energy demand, and low instrumental requirement. Moreover, it reduces significantly the process time as compared to conventional heating methods.

1*H*-Pyrazole-1-carboxamidine (PyzCA) is quite often employed to guanylate amines for the purpose of synthesizing bioactive compounds sometimes with complicated chemical structures, since the guanylation proceeds with high yield and selectivity [23–30]. However, it requires, in general, solvent and base. On the other hand, guanylation of amines with S-substituted

* Corresponding author.
E-mail address: mitue@belle.shiga-med.ac.jp (M. Fujita).

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isothiouronium salt (MeITU) is one of the most often used method to obtain substituted guanidines [15–22]. It is generally carried out using polar solvents such as water and alcohols with an excess of base under reflux conditions for a long period of time. Thus, both methods with above guanylating reagents have much room for improvement, especially in light of green process.

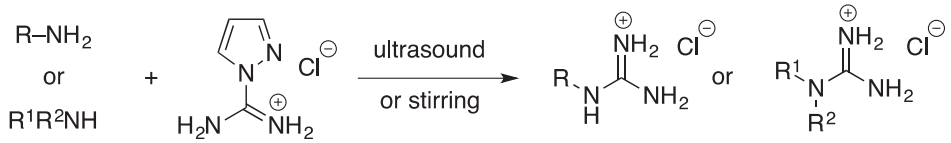
In the present work, we have explored the application of ultrasound to guanylation of amines with PyzCA or MeITU. We have found that the guanylation proceeds under solvent-free conditions when ultrasound was applied. In addition, the guanylation does not require base in most cases.

2. Results and discussion

We first chose guanylation of cyclohexylamine using PyrCA to see how it works to apply ultrasound to the mixture (Table 1, entries 1–3). The reaction was almost completed (97% yield) within 1.5 h at 25 °C under ultrasound irradiation with a high frequency of 480 kHz, while the yield reached only 63% with magnetic stirring instead of ultrasound irradiation. The guanylation was thus accelerated by ultrasound irradiation. The high frequency ultrasound promoted the reaction to a certain extent than the low frequency ultrasound, although the effect does not seem clear. We then investigated the guanylation of various amines using PyzCA, as shown in Table 1. Guanylations of primary amines with a primary alkyl group completed within 0.17 h (10 min) with magnetic stirring, so that the effect of ultrasound could not be confirmed (entries 4 and 5). 1-octadecanamine (stearylamine) is a primary amine with a long alkyl chain. Nevertheless, its guanylation was much slower than that of 1-octanamine (entry 6). This is probably because 1-octadecanamine exists in solid state (m.p. 50–52 °C). It is well-known that ultrasound irradiation on heterogeneous, solid-liquid mixture often accelerates organic reactions, while application of ultrasound on solid-solid mixture does not work out well [37]. 2-Octanamine, a primary amine with a secondary alkyl group, gave a similar result to that for cyclohexylamine, *i.e.*, ultrasound irradiation accelerated the guanylation when compared to that with magnetic stirring (entries 7–8). Piperidine, a cyclic secondary amine, was guanylated with a little acceleration by ultrasound (entry 9). Guanylation of dibutylamine, a secondary amine with two alkyl chains, proceeded slower than that of piperidine (entry 10). This is probably because that the steric hindrance of secondary amine with two alkyl chains is larger than that with a cyclic secondary amine structure, as is often observed in organic reactions. Aniline was hardly guanylated, arising from the low nucleophilicity of the aromatic amino group (entry 11). Application of ultrasound resulted in lowering the yield, although the reason is not clear at present. Unexpectedly, guanylation of 4-methoxyaniline (*p*-anisidine) was much accelerated by ultrasound (entries 12–14). Thus, no distinct frequency dependence was observed for the acceleration of the guanylation reactions, although it is proposed that ultrasound with frequency lower than 100 kHz mainly induces mechanical effects [45], while that with frequency higher than 100 kHz chiefly bring about chemical effects [46].

It is of great importance to compare our results with conventional methods using PyzCA in solution. For example, it was reported that *N*-cyclohexylguanidinium chloride was obtained in 84% yield by stirring a solution of cyclohexylamine, PyzCA, and diisopropylethylamine in DMF at ambient temperature for a few hours [23], while we demonstrated here that the yield was increased up to 97% by ultrasound application on a mixture of cyclohexylamine and PyzCA for few hours, as described above (entry 3). Thus, the ultrasound method gave higher yields than the conventional methods in most cases (cyclohexylamine [23,29], 2-ethanolamine [23], 1-octanamine [30], piperidine [23], 4-methoxyaniline [23]), except for aniline [23]. Another interesting point is that the ultrasound method does not require base for activating the reaction, in contrast to the conventional methods which often require organic

Table 1
Guanylation of various amines using 1*H*-pyrazole-1-carboxamidine hydrochloride (PyzCA) at 25 °C.[a]



Entry	Amine[b]	Time (h)	US_{LF}[d]	Yield (%)[c] US_{HF}[e]	Stirring[f]
1	Cyclohexylamine (−18)	0.5	49	82	
2		1.0	92	88	
3		1.5		97(93)	63
4	2-Ethanolamine (10)	0.17	95	98	99
5	1-Octanamine (−5 to −1)	0.17	95	98(99)	99
6	1-Octadecanamine (50–52) (Stearylamine)	3	24	48	40
7	2-Octanamine[g]	0.5	78	72	
8		1	89	89	65
9	Piperidine (−7)	0.5	95	89	83
10	Dibutylamine (−62)	3	14	17	21
11	Aniline (−6)	2	4	7	24
12	4-Methoxyaniline (56–59)	1.5	81	68	
13	(*p*-anisidine)	2	86		
14		3		91	50

[a] Amine (1.0 mmol); PyzCA (1.05 mmol).
[b] Melting point (°C) of the amine is in the parenthesis.
[c] Estimated by GC based on the formation of 1*H*-pyrazole. Isolated yield is in the parenthesis.
[d] Ultrasound with a low frequency of 36.6 kHz was applied.
[e] Ultrasound with a high frequency of 480 kHz was applied.
[f] Reaction mixture was magnetically stirred.
[g] Oil at room temperature.