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Generation of hazardous methyl azide and its application to synthesis of a key-intermediate of picarbutrazox, a new potent pesticide in flow

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ABSTRACT

Generation and reactions of methyl azide (MeN_3) were successfully performed by using a flow reactor system, demonstrating that the flow method serves as a safe method for handling hazardous explosive methyl azide. The reaction of NaN_3 and Me_2SO_4 in a flow reactor gave a MeN_3 solution, which was used for Huisgen reaction with benzoyl cyanide in a flow reactor after minimal washing. The resulting 1-methyl-5-benzoyltetrazole serves as a key intermediate of picarbutrazox (IX), a new potent pesticide.

1. Introduction

Tetrazoles[1] are synthetic heterocycles which have been used in a variety of fields[2] including organic chemistry, coordination chemistry, photographic industry, medicinal chemistry, and explosive production. 5-Substitited-1H-tetrazoles[3] serve as core structures of pharmacologically important compounds[4] such as Losartan,[5] Tomelukast,[6] AMPA antagonist,[7] Ciglitazone analogues,[8] and NMDA antagonist.[7] 1,5-Disubstituted tetrazoles also show remarkable physiological activities in spite of the lack of acidic N—H.[9] In particular, Picarbutrazox attracts much research interests because it is active against *P. viticola*, and *P. Infestans*. The spectrum also includes *Pythium* species which are responsible for damping-off disease in many crops.[10] For this reason, many picarbutrazox analogues have been developed and patented.[11] The late stage coupling of two advanced building blocks, the pyridine carbamate and 1-methyl-5-tetrazolyloxime which can be easily synthesized from 1-methyl-5-benzoyltetrazole, is advantageous from view points of convergentness and costs (Fig. 1).[10a]

Various methods for synthesizing 1-methyl-5-benzoyltetrazole have been developed so far. Conventionally, 1-methyl-5-benzoyltetrazole has been prepared by three-step synthesis via methylation of unsubstituted tetrazole (Fig. 2a).[12] However, this approach suffers from the regioselectivity problem in the lithiating step, which eventually leads to difficulty in purification of the product. Regioselective synthesis from mandelic acid has been developed

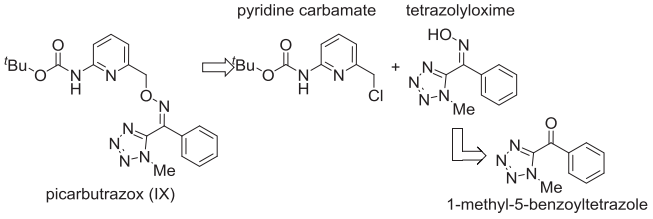

Fig. 1. Retrosynthetic strategy for Picarbutrazox having fungicidal activity.

(Fig. 2b), but this method requires five steps.[13] Another options is the three-component coupling reaction of methyl isonitrile, NaN_3 and benzoyl chloride (Fig. 2c).[14] However, the use of methyl isonitrile is problematic because of its strong smell. Also, methyl isonitrile is not commercially available. Another method which uses ammonium azide and diazomethane is also problematic because of a risk of explosion and the use of toxic chromium trioxide (Fig. 2d).[15] Therefore, a more efficient method for synthesizing 1-methyl-5-benzoyltetrazole is highly desired.

Generation of MeN_3 from NaN_3 and sulfuric acid ester followed by cyclization (Huisgen reaction) with benzoyl cyanide provides a simple two-step synthesis of 1-methyl-5-benzoyltetrazole (Fig. 3).[16] However, the use of MeN_3 is problematic, because of the danger of explosion.[17] Also, MeN_3 is rather difficult to handle because of its low boiling point (20 °C).[18] In fact, a special batch device for high-pressure reactions is often required for generation and reactions of MeN_3. In addition, the use of sulfuric acid ester and HN_3 generated by hydrolysis of NaN_3 is also dangerous.

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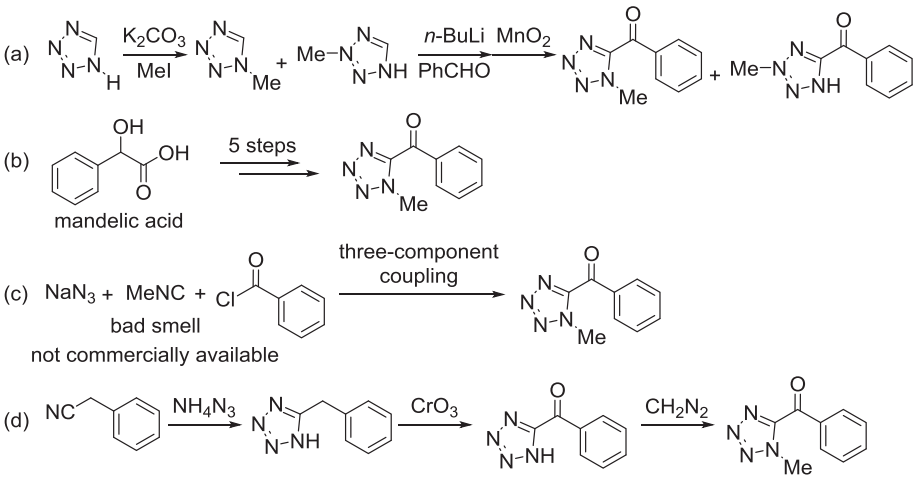

Fig. 2. Previous reports on synthesis of 1-methyl-5-benzoyltetrazole.

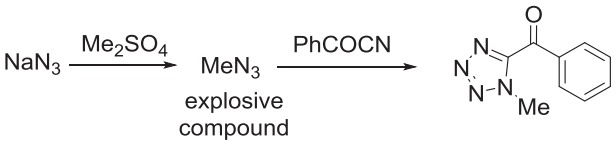

Fig. 3. Synthesis of 1-methyl-5-benzoyltetrazole.

Recently, chemical synthesis and production in flow reactors have received research interests from both academia and industry.[19–21] Enhanced heat and mass transfers, and the ability of controlling the residence time add great values to this technology. In addition, process operation in high-temperature/high-pressure conditions can readily be achieved.[22] Moreover, the risks associated with the use of hazardous materials can be minimized because only small quantities of reagents and products are exposed to the reaction conditions at any given time, making transformations using flow systems much safer.[23]

Although flow generation and reactions of hazardous HN_3, which can be used for synthesis of 5-substitited-1H-tetrazoles, have been studied extensively,[24] to the best of our knowledge, flow generation and reactions of MeN_3 has not yet been reported. Herein, we show that generation of MeN_3 followed by the reaction with benzoyl cyanide can be effectively conducted by using a flow reactor.

2. Results and discussion

A flow reactor system consisting of two pre-heating units (**P1** (ϕ = 1000 μm, L = 4 m), and **P2** (ϕ = 1000 μm, L = 4 m)), a T-shaped mixer (**M**), three tube reactors (**R1**, **R2**, and **R3**), and a back-pressure regulator was used (Fig. 4). A mixture of NaN_3 (1.0–4.0 M) and NaOH (0.20–0.60 M) in water, and a solution of dimethyl sulfate (3.5–9.0 M) in toluene were introduced to **M** (ϕ = 1.3 mm) by using plunger pumps. The resulting solution was passed through **R1** (ϕ = 1.0 mm, L = 1.0 m) and **R2** (ϕ = 2.18 mm, L = 10 m) in oil bath (*T* °C). The product solution was then passed through **R3** (ϕ = 2.18 mm, L = 6.0 m) which was cooled in an ice-water bath (0 °C) to stop the reaction. The pressure of the whole system was regulated by using a back-pressure regulator (0.9 MPa). After a steady state was reached, an aliquot of the product solution was taken for 5 min. MeN_3 is present mainly in the organic layer, although a small amount of MeN_3 is present in the aqueous layer as well. The yield of MeN_3 was determined by HPLC analysis of the both layers. Total yields are shown in Table 1 (See also Table 2 in the Section 4). The conversion of NaN_3 was also determined by HPLC analysis of the aqueous layer. The results obtained under various conditions are summarized in Table 1.

The yield of MeN_3 increased with an increase in the temperature (Table 1, entries 1–5). In addition, the increase in the $NaOH/Me_2SO_4$ ratio caused a decrease in the yield presumably because of hydrolysis of Me_2SO_4 by an excess amount of NaOH (Entries 6–8). In general, it is known that NaN_3 is converted to HN_3 under acidic conditions and that HN_3 is explosive even at room temperature. From a viewpoint of process safety management, appropriate pH control of the aqueous outlet solution is very important. Therefore, the amount of sodium hydroxide and dimethyl sulfate as well as their ratio were examined (Entries 9–12). As shown in entry 12, the use of 0.15 equivalents of NaOH and 1.1 equivalents of Me_2SO_4 made the outlet aqeuous solution neutral.

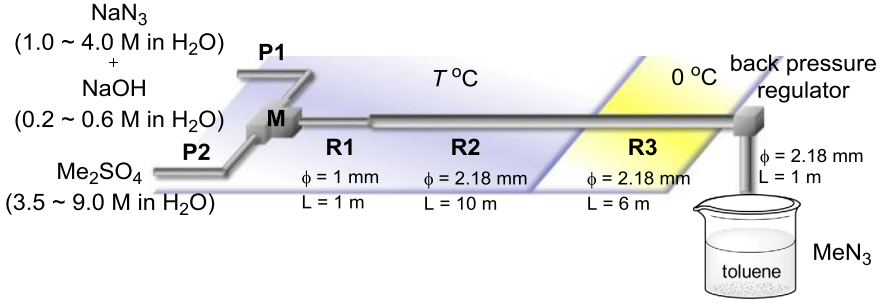

Fig. 4. A schematic diagram of the flow system for generation of MeN_3.

Table 1
Effect of the temperature and the amounts of NaOH and Me_2SO_4.

Entry	*T* (°C)	NaOH (eq)	Me_2SO_4 (eq)	Reaction time (min)	Conversion of NaN_3 (%)	Yield of MeN_3[a] (%)	pH
1	60	1.2	2.0	2.5	45	39	14.2
2	80	1.2	2.0	2.5	73	70	14.2
3	100	1.2	2.0	2.5	81	77	13.1
4	100	0.22	1.2	1.4	85	80	8.0
5	120	0.22	1.2	1.4	88	83	5.3
6	120	0.70	1.1	1.3	70	54	12.8
7	120	0.70	1.2	1.3	75	63	12.6
8	120	0.70	1.5	1.3	85	74	11.3
9	120	0.05	1.1	1.3	91	80	4.7
10	120	0.05	1.2	1.3	91	84	1.1
11	120	0.05	1.3	1.3	90	82	0.9
12	120	0.15	1.1	1.3	86	81	7.4

[a] The total yield of MeN_3 in both the organic and aqueous layers.

Table 2
The detailed conditions and results of the experiments shown in Table 1.

Entry	*T* (°C)	NaN_3 (mol/L)	Me_2SO_4 (mol/L)	NaN_3 (mL/min)	Me_2SO_4 (mL/min)	R2 ϕ (mm)	R2 L (m)	MeN_3 (%)		NaN_3 recovery (%) aqueous layer
								Organic layer	Aqueous layer	
1	60	2.0	4.0	9.8	4.9	2.18	10.0	39	0	55
2	80	1.0	4.0	9.8	4.9	2.18	10.0	62	8	27
3	100	1.0	4.0	9.8	4.9	2.18	10.0	67	10	19
4	100	2.0	4.0	25.1	15.0	3.76	5.0	73	7	15
5	120	2.0	4.0	25.1	15.0	3.76	5.0	75	8	12
6	120	3.5	3.5	11.0	11.5	2.18	8.0	51	3	30
7	120	3.5	3.5	10.0	12.5	2.18	8.0	60	3	25
8	120	3.5	3.5	9.0	13.5	2.18	8.0	71	3	15
9	120	4.0	9.0	15.4	7.2	2.18	8.0	74	6	9
10	120	4.0	9.0	14.8	7.9	2.18	8.0	78	6	9
11	120	4.0	9.0	14.2	8.2	2.18	8.0	76	6	10
12	120	2.5	4.0	26.0	17.0	3.76	5.0	75	7	14

[a]The total yield of MeN_3 in both the organic and aqueous layers.

Next, we examined a continuous operation of the reaction under the optimized conditions (entry 12 in Table 1, NaOH (0.15 eq) and Me_2SO_4 (1.1 eq)). The operation for 10 min at the total flow rate of 43 mL/min yielded 39 g of MeN_3 (82% yield) in the organic layer. In general, the productivity of a flow reaction can be increased by increasing the flow rate, which is one of the most advantageous features of flow processes over batch processes. The operation at a higher total flow rate (69 mL/min) was successfully carried out for 61 min to yield 383 g of MeN_3 (82% yield) in the organic layer, indicating the feasibility of the production on a large scale (9.1 kg/day).

Notably, a high concentration solution of MeN_3 (23.9 wt%) in toluene was obtained by using the present method. After washing with NaOH*aq* and H_2O, the solution was diluted with toluene to obtain a 12.0 wt% solution, which was directly used, without further purification, for the subsequent Huisgen reaction with benzoyl cyanide. A flow reactor system consisting of two pre-heating units (**P1** (ϕ = 1000 μm, L = 4 m) and **P2** (ϕ = 2.18 mm, L = 4 m)), a T-shaped mixer (**M**), three tube reactors (**R1**, **R2**, and **R3**), and a back-pressure regulator was used. A mixture of MeN_3 (12.0 wt%) and PhCOCN (28.9 wt% (1.05 eq)) in toluene (flow rate: 2.8 mL/min) was passed through **R1** (ϕ = 3.36 mm, L = 20.5 m, 65 min) in oil bath (200 °C). The resulting solution was further diluted with toluene (flow rate: 6.35 mL/min) in **M** (ϕ = 2.3 mm). The resulting solution was passed through **R2** (ϕ = 3.36 mm, L 0.5 m, 0.5 min) at 200 °C and was passed through **R3** (ϕ = 4.35 mm, L = 10 cm) at room temperature to stop the reaction. The resulting solution was poured into a collector through a back-pressure regulator (8 MPa) and a tube (ϕ = 2.18 mm, L = 2.0 m). After a steady state was reached, an aliquot of the product solution was taken for 15 min. 1-Methyl-5-benzoyltetrazole was obtained in 78% yield (12.1 g), which can be easily converted into picarbutrazox (IX), a new pesticide. It should be emphasized that the reaction using the flow reactor was conducted safety even at a high temperature (200 °C) and a high pressure (8 MPa) (Fig. 5).

3. Conclusion

The results described above indicate that the flow method serves as an effective and safe tool for generation and reactions of haza6rdous MeN_3. 1-Methyl-5-benzoyltetrazole which is a key intermediate of picarbutrazox (IX), a new pesticide, was successfully synthesized by the flow reaction of MeN_3 and benzoylnitrile. This study speaks well for the potentiality of flow microreactor systems for large-scale production of chemicals using hazardous compounds. Further work aimed at industrial sacle production is currently in progress.

4. Experimental section

4.1. General

Stainless steel (SUS316) union mixers with inner diameter of 1.3 and 2.3 mm were manufactured by BI-Lok Co., Inc. Stainless steel (SUS304) tube reactors with inner diameter of 1.0, 2.18 and 3.76 mm were purchased from KUZE Co. Ltd. The mixer and tube reactors were connected with stainless steel fittings (BI-Lok Co., Inc., 1/16, 1/8, 3/16 and 1/4OUW). The flow system was dipped in an oil bath to control the temperature. Solutions were introduced to the flow reactor system using plunger pumps (NIHON SEIMITSU KAGAKU Model NP-FX-60 and SHIMADZU Model

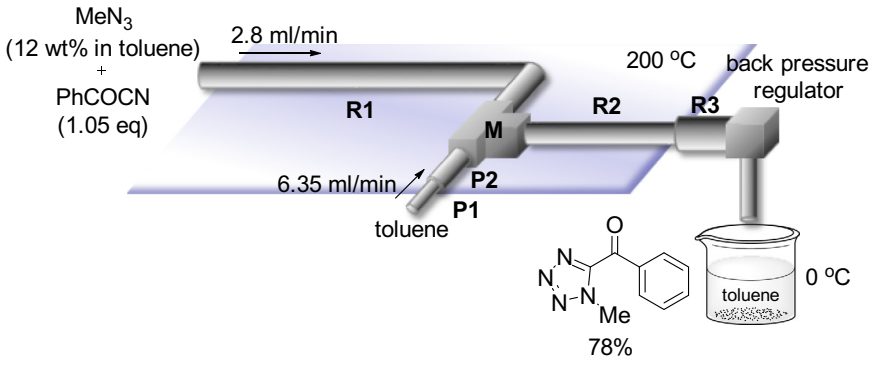

Fig. 5. A schematic diagram of the flow system for synthesis of 1-methyl-5-benzoyltetrazole.

LC-10AS). TESCOM Model 44-2300 series or 26-1700 Series were used as back pressure valve.

HPLC analyses for MeN_3 and NaN_3 were performed on a SHIMADZU LC-20AT liquid chromatograph equipped with a UV detector using a HPLC column (Waters X-bridge BEH C18 Column, 5 μm, 4.6 mm × 250 mm; oven temperature, 40 °C; flow rate 1.0 ml/min (CH_3CN:H_2O:KH_2PO_4:SDS:10% H_3PO_4 = 400:600:1.2:1.0:0.5 (v/v/wt/wt/v))). HPLC yield was determined by using ethyl benzoate, t^R (15.2 min) as an internal standard.

HPLC analysis for 1-methyl-5-benzoyltetrazole was performed on a SHIMADZU LC-10AT liquid chromatograph equipped with an UV detector using a HPLC column (GL-Science Nucleosil 100-5CN Column, 5 μm, 4.6 mm × 250 mm; t^R (1-methyl-5-benzoyltetrazole) 15.3 min, t^R (PhCOCN) 5.2 min; oven temperature, 40 °C; flow rate 1.0 ml/min (hexane: ethyl acetate = 20:1). The yield of 1-methyl-5-benzoyltetrazole was determined by using methyl-o-anisate, t^R (9.8 min) as an internal standard (78%, 12.1 g). GC analysis of unchanged MeN_3 was performed on a SHIMADZU GC-14B gas chromatograph equipped with a flame ionization detector using packed column (Gaskuropack 5480/100). (t^R (MeN_3) 4.7 min; initial oven temperature, 100 °C for 10 min; rate of temperature increase, 5 °C/min)) using acetonitrile t^R (9.2 min) as an internal standard.

^1H and ^{13}C NMR spectra were recorded on JOEL-400 (^1H 400 MHz and ^{13}C 100 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$. NaN_3, dimethyl sulfate, and toluene were purchased from Wako Co., Inc. Benzoyl cyanide was purchased from Zaoyang Xianfei High-tech Pesticide Co., Ltd, and was distilled before use.

4.2. Synthesis of MeN_3 using the flow system

A flow reactor system consisting of two pre-heating units (**P1** (ϕ = 1000 μm, L = 4 m), and **P2** (ϕ = 1000 μm, L = 4 m)), a T-shaped mixer (**M**), four tube reactors (**R1**, **R2**, and **R3**), and a back-pressure regulator was used. A mixture of NaN_3 (1.0–4.0 M) and NaOH (0.20–0.60 M) in water, and a solution of dimethyl sulfate (3.5–9.0 M) in toluene were introduced to **M** (ϕ = 1.3 mm) by using plunger pumps. The resulting solution was passed through **R1** (ϕ = 1.0 mm, L = 1.0 m) and **R2** (ϕ = 2.18 mm, L = 10 m) in oil bath (*T* °C), and was then passed through **R3** (ϕ = 2.18 mm, L = 6.0 m) in ice-water bath (0 °C) to stop the reaction. The resulting solution was collected through a back-pressure regulator (0.9 MPa) and a tube (ϕ = 2.18 mm, L = 1.0 m). After a steady state was reached, an aliquot of the product solution was taken for 5 min. Then, after the reaction solution was separated into an organic layer and an aqueous layer, the yield of MeN_3 was determined by HPLC analysis of the organic layer (reversed phase chromatography, wavelength = 210 nm, t^R 4.5 min). The conversion of NaN_3 was determined by HPLC analysis of the aqueous layer (reversed phase chromatography, wavelength = 210 nm, t^R 3.1 min). The results obtained with different temperatures, amounts of sodium hydroxide, and amounts of dimethyl sulfate are summarized in Tables 1 and 2. The spectral data were identical to those reported in the literature.[18]

4.3. Continuous operation of the flow synthesis of MeN_3

A flow reactor system consisting of two pre-heating units (**P1** (ϕ = 1000 μm, L = 4 m), and **P2** (ϕ = 1000 μm, L = 4 m)), a T-shaped mixer (**M**), four tube reactors (**R1**, **R2**, **R3**, and **R4**), and a back-pressure regulator was used. A mixture of NaN_3 (4.0 M) and sodium hydroxide (0.60 M) in water (21 or 34 ml/min), and a solution of dimethyl sulfate (4.0 M) in toluene (22 or 35 ml/min) were introduced to **M** (ϕ = 1.3 mm) by using plunger pumps. The resulting solution was passed through **R1** (ϕ = 1.0 mm, L = 1.0 m) and **R2** (ϕ = 3.76 mm, L = 5 m (21 and 22 ml/min) or 8 m ((34 and 35 ml/min))) in oil bath (120 °C), and was then passed through **R3** (ϕ = 2.18 mm, L = 6.0 m) in ice-water bath (0 °C). The resulting solution was collected through a back-pressure regulator (0.9 MPa) and a tube (ϕ = 2.18 mm, L = 2.0 m). After a steady state was reached, an aliquot of the product solution was taken for 10 min or 61 min. After the reaction solution was separated into organic layer and aqueous layer, the yield of MeN_3, and the conversion of NaN_3 were determined by HPLC.

4.4. Synthesis of 1-methyl-5-benzoyltetrazole using the flow system

A flow reactor system consisting of a T-shaped mixer (**M**), four tube reactors (**R1**, **R2**, and **R3**), and a back-pressure regulator was used. A mixture of MeN_3 (12.0 wt%) and PhCOCN (28.9 wt% (1.05 eq)) in toluene (flow rate: 2.8 mL/min) was passed through **R1** (ϕ = 3.36 mm, L = 20.5 m, 65 min) in oil bath (200 °C). The resulting solution was further diluted with toluene, which was preheated through two pre-heating units (**P1** (ϕ = 1000 μm, L = 4 m) and **P2** (ϕ = 2.18 mm, L = 4 m)) (flow rate: 6.35 mL/min) in **M** (ϕ = 2.3 mm). The resulting solution was passed through **R2** (ϕ = 3.36 mm, L = 0.5 m, 0.5 min) at 200 °C and was passed through **R3** (ϕ = 4.35 mm, L = 10 cm) at room temperature to stop the reaction. The product solution was collected through a back-pressure regulator (8 MPa) and a tube (ϕ = 2.18 mm, L = 2.0 m). After a steady state was reached, an aliquot of the product solution was taken for 15 min. The amounts of unchanged MeN_3 (13%) and PhCOCN (12%) were determined by GC-FID analysis. The yield of 1-methyl-5-benzoyltetrazole[12b] was determined by HPLC analysis. ^1H NMR (400 MHz, $CDCl_3$) 8.45 (dd, *J* = 6.4 Hz, 0.8 Hz, 2H), 7.72

(t, J = 7.2 Hz, 1H), 7.57 (dt, J = 7.6 Hz, 1.6 Hz, 2H), 4.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 36.8, 128.6, 130.8, 134.6, 134.9, 149.4, 181.0; MS (ESI) m/z calcd for $C_9H_8N_4O_1$ ($[M+H]^+$): 189.0771, found: 189.0767.

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