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Process Improvements for the Preparation of Insecticide Clothianidin

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This article describes the process improvements for the preparation of the insecticide clothianidin **1**. (Z)-1-Methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**9**) which was obtained by Mannich reaction of (Z)-1-methyl-2-nitroguanidine (**5**) *n*-Propylamine and 37 % aqueous formaldehyde solution in 97 % yield. Intermediate **9** was electrophilic substituted with 2-chloro-5-(chloromethyl)thiazole (**4**) in the presence of acid-binding agent to give (E)-1-[(2-chlorothiazol-5-yl)methyl]-3-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**10**) in 90 % yield. The target compound **1** was given by the hydrolyzation of **10** in 88 % yield. The optimized conditions for the preparation of clothianidin were obtained *via* screening the reaction temperature, reaction time, acid-binding and solvents in three steps. The overall yield of clothianidin **1** was up to 77 %.

Keywords: Insecticide, Clothianidin, Mannich reaction, Optimization.

INTRODUCTION

Neonicotinoids have been attracted with wide attention in both industry and academia because of their outstanding insecticidal activity[1]. Neonicotinoid insecticides have been rapidly developed worldwide for controlling insects because of their high potency, low mammalian toxicity, broad insecticidal spectra and good systemic properties. Neonicotinoids, which interact with nicotinic acetylcholine receptors (nAChR), have a higher affinity for the insect receptor than for the mammalian receptor[2-5] and are relatively safe toward mammals and aquatic life. So it has been made in a significant progress in the cloning of receptor sub-units, their expression *in vivo* and the pharmacology of the ligand-gated ion channel complexes[6-8]. Clothianidin **1** was the major active ingredient of the neonicotinoid class to reach market. So, most research on neonicotinoids has so far been performing clothianidin, as the representative. In this work, an improved synthesis method was introduced for the insecticide clothianidin (E)-1-(2-chloro-5-thiazolylmethyl)-3-methyl-*N*-nitroguanidine (**1**, Fig. 1).

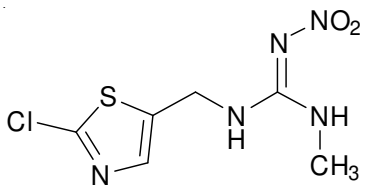

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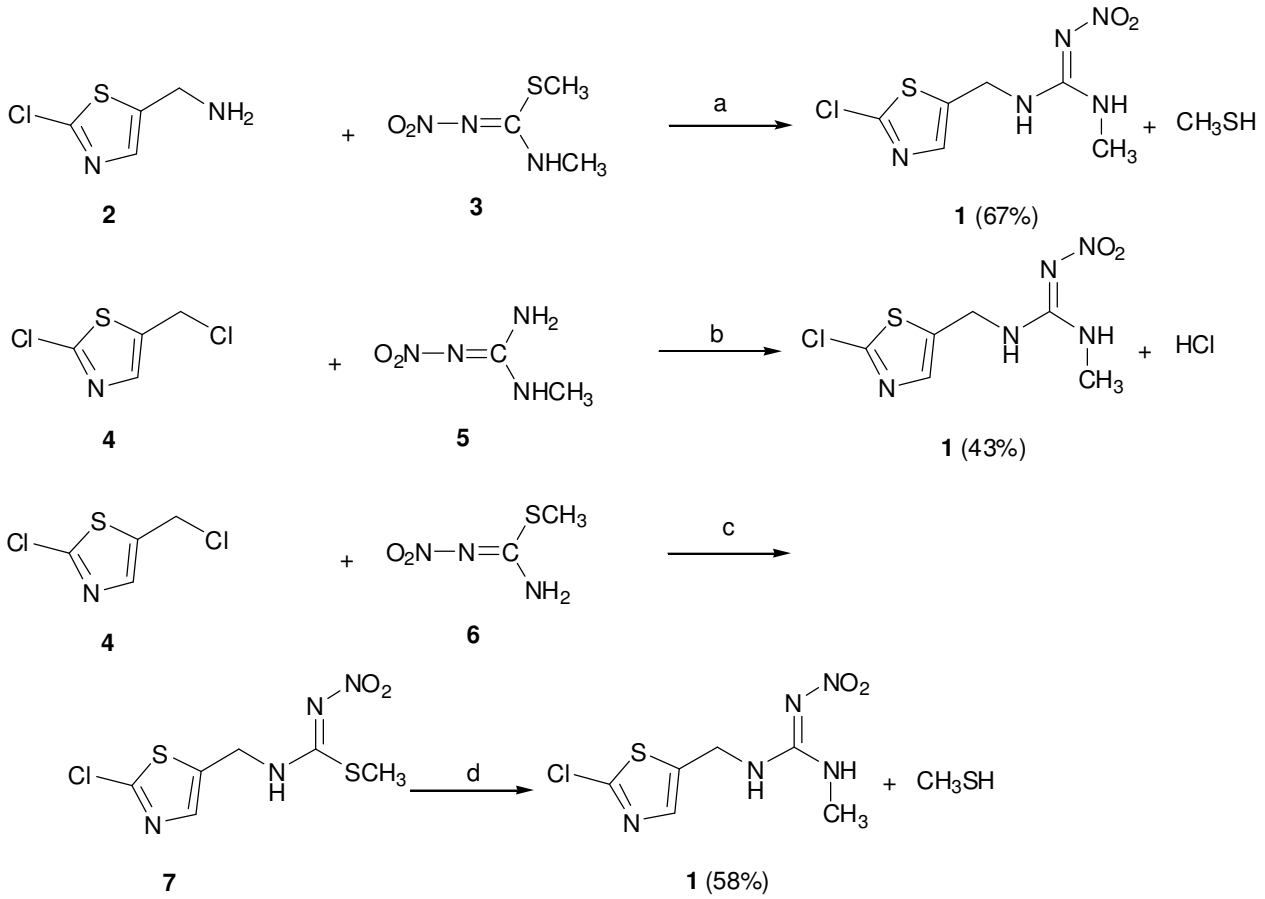
Fig. 1. Structure of compound **1**

Evidence in chronological order, synthetic routes of clothianidin **1** are divided into two generations. The first-generation synthetic method for clothianidin **1** has three process routes **(Scheme-I)**. The first, clothianidin **1** was obtained by electrophilic substitution of (2-chlorothiazol-5-yl)methanamine (**2**) and S-methyl-*N*-methyl-*N*'-nitroisothiourea (**3**) in 67 %[9]. The second, 2-chloro-5-(chloromethyl)thiazole (**4**) was electrophilic substitution with *N*-methyl-*N*'-nitroguanidine (**5**) in the presence of catalytic agent to give clothianidin (**1**) in 43 % yield[10,11]. The third, (Z)-1-((2-chlorothiazol-5-yl)methyl)-2-methyl-3-nitroisothiourea (**7**) was obtained by the electrophilic substitution of compound **4** and S-methyl-N-nitroisothiourea (**6**), then was aminomethylation with methylamine to afford clothianidin **1** in 58 % yield[12,13]. The first-generation synthetic method is associated with several drawbacks, as summarized below:

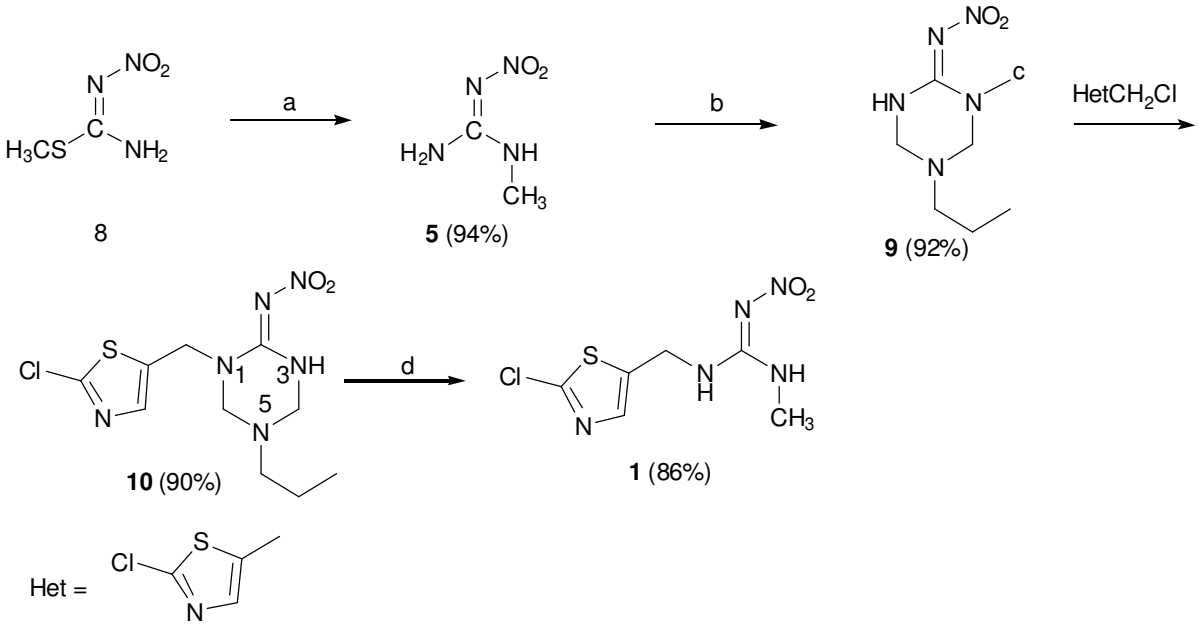
(a) Various steps (steps b, c and d) requires purification by SiO_2 column chromatography, (b) Yield of compound **1** is low, (c) Preparation of **1** *via* isothiourea **3**, **7** is undesirable from the point of view of environmental protection,

Further, the second-generation synthetic method was constructed *via* alkylation of the nitroimino-hexahydro-triazine (**9**) with heteroaryl-methyl chlorides (**10**) **(Scheme-II)**[14]. This method also has some shortcomings, *viz*., (a) Step c requires chromatographic separation, (b) Low reproducibility of the electrophilic substitution reaction might be a significant issue for large-scale synthesis and (c) Low yield in each step.



Reagents and conditions: (a) EtOH, reflux, 6 h, SiO_2 column chromatography, (b) CsCl (cat.), PTC, DMF, 25 ℃, 24 h, SiO_2 column chromatography, (c) CsCl (cat.), PTC, EtOH, 50 ℃, 18 h, SiO_2 column chromatography, 75.00 % yield, (d) K_2CO_3, CH_3NH_2, DMF, 40 ℃, 12 h, SiO_2 column chromatography, 77.33 %.

Scheme-I: First-generation synthetic method



Reagents and conditions: (a) CH_3NH_2, EtOH, 80 ℃, 16 h, then cool to 25 ℃, (b) *n*-$PrNH_2$, EtOH, 37 % aqueous formaldehyde solution, 50 ℃, 5 h, then cool to 25 ℃, (c) $HetCH_2Cl$, K_2CO_3, DMF, 50 ℃, 16-20 h, SiO_2 column chromatography, (d) aq 1N HCl, EtOH, 25 ℃, 24h

Scheme-II: Second generation synthetic method

Under those circumstances, the development of a suitable process for **1** with higher overall yield and without SiO_2 column chromatography purification was demanded. Our efforts has been focusing on designing a safe and efficient synthesis method of **1** that incorporates the following key characteristics: (1) group-protecting technology, (2) optimized conditions. During this research, *N*-methyl-*N'*-nitroguanidine (**5**) could be purchased as a commercially available compound. The process improvements for the preparation of the insecticide clothianidin **1** was introduced in this work.

EXPERIMENTAL

Starting materials, solvents and reagents were purchased from commercial sources and were used as received without further purification. Reactions were monitored by reversephase HPLC on a DIONEX chromatograph. HPLC purity refers to chromatographic area percentage. NMR spectra were recorded on a Bruker 400 spectrometer and the chemical shifts were reported in ppm with the solvent resonance as the internal standard (^{1}H, $CDCl_3$: 7.26; DMSO-d_6: 2.50. ^{13}C, $CDCl_3$: 77.0, DMSO-d_6: 39.5).

Synthesis of (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (9): A mixture of the *N*-methyl-*N'*-nitroguanidine (**5**) (0.1 mol), *n*-propylamine (0.1 mol) and 15.2 mL of 37 % aqueous formaldehyde solution (0.2 mol) in methanol (50 mL) were heated to certain temperature for some time. The reaction progress was monitored by HPLC until the starting material was consumed (≤ 0.50 %). After being cooled to 0 °C, the products precipitated out of the reaction mixture. Filtration afforded the products in pure form (Table-1). m.p. 85-86 °C (Lit.[10] 84-86 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.24 (bs, 1H), 4.31 (s, 2H), 4.29 (s, 2H), 2.86 (s, 3H), 2.57 (t, *J* = 2H), 1.42-1.54 (m, 2H), 0.88 (t, *J* = 6, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.1, 67.7, 59.4, 51.8, 33.9, 20.4, 11.4.

Synthesis of (E)-1-[(2-chlorothiazol-5-yl)methyl]-3-methyl-*N*-nitro-5-propyl -1,3,5-triazinan- 2-imine (10): A solution of (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**9**) (15.3 g, 0.075 mol), base (0.186 mol) in a solvent (100 mL) was added over 20 min to the slurry of 2-chloro-5-(chloromethyl) thiazole (**4**) (15.3 g, 0.075 mol) in typically solvent (50 mL) at < 30 °C. The reaction progress was monitored by HPLC until consumption (20-24 h) of starting material (≤ 0.50 %) and then cooled to 10 °C. After the filtration and the concentration, the crude product was recrystallized from methanol to afford compounds **10** (Tables 2 and 3). m.p. 84-85 °C (Lit.[10] 84-85 °C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.69 (s, 1H), 4.71 (s, 2H), 4.44 (d, 4H), 2.86 (s, 3H), 2.44 (t, *J* = 7.35 Hz, 2H), 1.34 (tq, Jt = Jq = 6 Hz, 2H), 0.78(t, J = 7.33 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.0, 151.6, 141.5, 68.5, 64.4, 51.9, 43.1, 34.7, 20.2, 11.2.

Synthesis of (E)-1-(2-chloro-5-thiazolylmethyl)-3-methyl-*N*-nitroguanidine (1): Certain quantity of acid was added to a solution of compound **10** (0.015 mol) in MeOH (30 mL) over 20 min at 21-25 °C. The reaction mixture was stirred at 21-25 °C until raw material **10** cannot be further consumed by HPLC analysis. Then cooled to 0 °C, the crystallized product out of the reaction mixture. The reaction mixture was then filtered and the product cake was washed with *n*-heptane (20 mL). The wet cake was dried under vacuum at 40-45 °C afford the desired product **1** (Tables 4 and 5) as a white solid. m.p. 174-175 °C (Lit.[10] 174-175 °C); ^{1}H NMR (500 MHz, DMSO-d_6): 9.11 (bs, 1H), 7.94 (bs, 1H), 7.59 (s, 1H), 4.50 (bd, *J* = 4.75 Hz, 2H), 2.81 (bd, *J* = 4.75Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 157.3, 150.7, 139.9, 37.2, 28.3.

RESULTS AND DISCUSSION

Optimization for Mannich reaction: The (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**9**) was prepared by Mannich reaction of N-methyl-*N'*-nitroguanidine (**5**), *n*-propylamine and 37 % aqueous formaldehyde solution. The optimized conditions for preparation of compound **9** were obtained *via* screening the temperatures, time and solvents.

Firstly, several tests were performed to optimize the temperatures (Table-1). When the reaction time was 6 h, using methanol or ethanol as solvent, temperatures screening was done among 45, 50, 55 °C and 60 °C (entries 1, 2, 3 and 4; 5, 6, 7 and 8). Results showed that 55 °C (entry 3) gave the best results in comparison with other temperatures such as 45 °C (entries 1, 5), 50 °C (entries 2, 6) and 60 °C (entries 4, 8). As expected, better results would be obtained by modifying reaction temperatures.

TABLE-1
TEMPERATURES, TIME AND SOLVENTS SCREENING FOR MANNICH REACTION[a]

Entry	Temp. (°C)	Time (h)	Solvent (100 mL)	HPLC area (%)	
				9	5
1	45	6	Methanol	95.62	4.38
2	50	6	Methanol	95.89	4.11
3	55	6	Methanol	97.57	2.43
4	60	6	Methanol	96.01	3.99
5	45	6	Ethanol	92.43	7.57
6	50	6	Ethanol	93.14	6.86
7	55	6	Ethanol	94.10	5.90
8	60	6	Ethanol	93.65	6.35
9	55	24	Methanol	97.26	2.74
10	55	24	Ethanol	93.72	6.28
11	55	18	Methanol	97.49	2.51
12	55	18	Ethanol	94.01	5.99
13	55	7	Methanol	97.53	2.47
14	55	7	Ethanol	94.07	5.93
15	55	5	Methanol	95.33	4.67
16	55	5	Ethanol	93.64	6.36
17	55	4	Methanol	93.70	6.30
18	55	4	Ethanol	93.51	6.49
19	55	2	Methanol	90.79	9.21
20	55	2	Ethanol	91.77	8.23
21	55	0.25	Methanol	84.60	15.40
22	55	0.25	Ethanol	72.30	27.70

[a]Reaction conditions: *N*-methyl-*N'*-nitroguanidine (0.2 mol), *n*-propylamine (0.2 mol), 37% aqueous formaldehyde solution (0.4 mol).

Furthermore, reaction time screening was done using 0.25, 2, 2.5, 4, 5, 6, 7, 18 and 24 h (Table-1, entries 3, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 and 22) at 55 °C, the experimental results were showed in Table-1 and the optimal reaction time was obtained at 6 h.

Besides the temperature and the reaction time, the effect of solvent was also investigated. Compared with ethanol, the experimental results showed that the methanol had a higher yield (entry 3).

In the second-generation synthesis, intermediate **9** was prepared in 92 % yield. However, we improved the yield to 97.57 % with some modifications of synthetic conditions. The reaction was stirred in the methanol at 55 °C for 6 h, which results in the highest yield of compound **9** (as shown in Table-1, entry 3).

Optimization of the reaction conditions of electrophilic substitution: Against the second-generation synthetic method, a robust, production process for **10** is desired with a higher overall yield that does not require column chromatography purification. After the filtration and the concentration, the crude product was recrystallized from methanol to afford compound **10** in pure form. The reaction of (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine **9** and 2-chloro-5-(chloromethyl)thiazole **4** was tested in the presence of various kinds of bases (Table-2). Most of the tested bases gave the complete conversion of **10**, except in the cases of sodium hydroxide and potassium hydroxide, which could produce a large quantity of unknown impurities. The results indicated that NaOH and KOH (entries **4** and **5**) could lead the fast decomposition reaction. The order of the substitution reaction rate was as follows: $K_2CO_3 > NaCO_3 > KHCO_3$. Further, solvent screening was done among THF, toluene, DMF, acetonitrile, *n*-butyl alcohol and ethanol (Table-3). Results showed that DMF was the best one.

TABLE-2
BASES SCREENING FOR ELECTROPHILIC SUBSTITUTION STEP[a]

Entry	Bases	HPLC area (%)			
		9	4	10	Uknown impurity
1	$KHCO_3$	12.90	7.17	79.03	0.90
2	K_2CO_3	4.70	4.36	90.01	0.30
3	$NaCO_3$	10.10	9.30	80.20	0.40
4	KOH	0.70	0.29	0	99.01
5	NaOH	0.25	0.04	0	99.71

[a]Reaction conditions: (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (0.076 mol), 2-chloro-5-(chloromethyl)thiazole (0.091 mol), DMF (100 mL), 50 °C, 20–24 h.

TABLE-3
SOLVENT SELECTION FOR THE PREPARATION OF 10[a]

Entry	Solvents (100 mL)	Conversion (% ; HPLC)
1	THF	55.80
2	Toluene	59.70
3	DMF	90.01
4	Acetonitrile	81.90
5	*n*-butyl alcohol	74.13
6	Ethyl alcohol	61.33

[a]Reaction conditions: (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (0.076 mol), 2-chloro-5-(chloromethyl)thiazole (0.091 mol), 50 °C, 24 h

Optimization of the reaction conditions of synthesis of 1: To complete the synthesis of the target compounds **1**, the N-CH_2-N bonds should be cleaved in the compounds **10**. The hydrolysis abilities of different kinds of acids such as HCl, H_3PO_4, H_2SO_4, CH_3COOH, CF_3COOH and methanesulfonic acid (MSA)) were investigated (Table-4). The results indicated that diluted HCl (entry 1), is more suitable used as the hydrolysis catalyst. Furthermore, the influence of different normalities (0.4, 0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 N) of HCl on the yield of **1** was tested at 20-25 °C (Table-5). The data showed that the reaction with 0.4 N (entry 1) or 1.6 N (entry 7) HCl for 24 h gave lower yield and when the reaction was carried out using 1 N HCl for 24 h, optimum results were obtained (entry 4).

TABLE-4
ACID SELECTION FOR THE PREPARATION OF 1[a]

Entry	Acid (30 mL), normality	HPLC area (%)	
		1	10
1	HCl, 1	88.20	11.80
2	H_3PO_4, 3	64.70	35.30
3	H_2SO_4, 2	70.30	29.70
4	CH_3COOH, 1	57.80	42.20
5	CF_3COOH, 1	45.10	54.90
6	MSA, 1	46.50	53.50

[a]**Reaction conditions:** (E)-1-((2-chlorothiazol-5-yl)methyl)-3-methyl-*N*-nitro-5- propyl- 1,3,5-triazinan-2-imine (0.038 mol), MeOH, 20-25 °C, 24 h, then cool to 0 °C

TABLE-5
INFLUENCE OF HCL QUANTITY ON YIELD OF 1[a]

Entry	HCl (mole ratio)	HPLC area (%)		Unknown impurity
		1	10	
1	0.4	57.80	37.65	4.55
2	0.6	64.70	30.52	4.78
3	0.8	76.30	19.03	4.67
4	1.0	88.20	7.31	4.49
5	1.2	85.14	7.03	7.83
6	1.4	79.56	8.92	11.52
7	1.6	70.47	11.57	17.96

[a]**Reaction conditions:** (E)-1-((2-chlorothiazol-5-yl)methyl)-3-methyl-*N*-nitro-5- propyl-1,3,5-triazinan-2-imine (0.038 mol), MeOH (30 mL), 20-25 °C, 24 h, then cool to 0 °C

Conclusion

An efficient three-step process was developed for the synthesis of clothianidin and the overall yield of the target product was increased from 66.90 to 77.00 % under the optimized conditions. The present work also described the procedure for the preparation of key intermediates such as (Z)-1-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**9**) and (E)-1-((2-chlorothiazol-5-yl)methyl)-3-methyl-*N*-nitro-5-propyl-1,3,5-triazinan-2-imine (**10**). Furthermore, effective purification of product makes the process easier to scaling-up.

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