



An Improved One-Pot Procedure for Preparation Of *N,N*-Diethyl-*m*-Toluamide from *m*-Toluic Acid

Procedimiento mejorado de un solo reactor para la preparación de *N,N*-dietil-*m*-toluamida a partir de ácido *m*-toluico

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ABSTRACT

Introduction: Recent statistics have shown that there are hundreds of diseases caused by insects that have a significant impact on human health and they are often fatal. Mosquitoes cause about 10 diseases, most notably malaria, dengue fever and zika fever. *N,N*-diethyl-*m*-toluamide (**1**, DEET) or *N,N*-diethyl-*m*-methylbenzamide was globally approved under brand names *m*-Dephene, Detamide, Flypel as one of the most prominent agents for preparation of insect repellants.

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Objectives: To present an enhanced method for synthesis of *N,N'*-diethyl-*m*-toluamide which can be introduced to industrial scale.

Method: The input materials: *m*-toluic acid has been activated with thionyl chloride to create the intermediate product, *m*-toluoyl chloride. This product then was reacted with diethylamine in order to produce DEET. This method has been improved the factors affecting the synthesis of DEET.

Results: DEET was successfully synthesized using well known materials with high efficiency and purity. During research all the by-products and waste materials in the reaction are highly water-soluble, therefore the final product was obtained at pharmaceutical requirement without further purification. The analytical data has shown that DEET was collected at a very high yield in the range of 96-98%, purity (HPLC): 95.5-97.6%. The structure of DEET was determined by model spectroscopies MS, and NMR.

Conclusions: An improved procedure for the synthesis of *N,N*-diethyl-*m*-toluamide (DEET) or *N,N*-diethyl-*m*-methylbenzamide is established where the use of all reagents was optimized in suitable amount to apply in industrial production.

Keywords: *m*-toluic acid; *N,N*-diethyl-*m*-toluamide; ingredient; insects repellent.

RESUMEN

Introducción: Las estadísticas recientes demuestran que hay cientos de enfermedades causadas por insectos, con impacto significativo en la salud humana, a menudo fatales. Los mosquitos causan unas 10 enfermedades, entre las que destacan la malaria, el dengue y el zika. El *N,N*-dietil-*m*-toluamida (**1**, DEET) o *N,N*-dietil-*m*-metilbenzamida fue aprobado a nivel mundial bajo las marcas *m*-Dephene, Detamide, Flypel como uno de los agentes más destacados para la preparación de repelentes de insectos.

Objetivos: Presentar un método mejorado para la síntesis de *N,N*-dietil-*m*-toluamida, que puede introducirse a escala industrial.

Método: Los materiales de entrada: el ácido *m*-toluico se activaron con cloruro de tionilo, para crear el producto intermedio, cloruro de *m*-toluilo. Este producto luego se hizo reaccionar con dietilamina para producir DEET. Este método ha mejorado los factores que afectan la síntesis de DEET.

Resultados: Se sintetizó DEET con éxito, utilizando materiales bien conocidos, con alta eficiencia y pureza. Durante esta investigación, todos los subproductos y materiales de desecho de la reacción son



altamente solubles en agua, por lo que el producto final se obtuvo según los requisitos farmacéuticos, sin purificación adicional. Los datos analíticos demostraron que DEET se recolectó con un rendimiento muy alto en el rango de 96-98 %, pureza (HPLC): 95,5-97,6 %. La estructura del DEET se determinó mediante espectroscopias modelo como MS, NMR.

Conclusiones: Se estableció un procedimiento mejorado para la síntesis de *N,N*-dietil-*m*-toluamida (DEET) o *N,N*-dietil-*m*-metilbenzamida, que optimizó el uso de todos los reactivos, en cantidad adecuada para aplicar en la producción industrial.

Palabras clave: ácido *m*-toluico; *N,N*-dietil-*m*-toluamida; ingrediente; repelente de insectos.

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INTRODUCTION

N,N-Diethyl-*m*-methylbenzamide is a well-known member in class of effective insects repellent with specific effects against blood-sucking insects.⁽¹⁾ In addition, many studies also have found that DEET could apply to another medicinal area as drug delivery agent.⁽²⁾ Since 1944, for over 7 decades, *N,N*-Diethyl-*m*-methylbenzamide (DEET) has been determined as one of the best reagents for insects repellent.⁽³⁾

Until now, there are a lot of research papers and patents that have reported the methods to synthesize amides, including DEET as well as their derivatives.^(4,5) However, the process to synthesize amides often performs by activating the carboxyl or amine group before using them to react.^(5,6,7) Among them, one of the most common procedures is the activation of carboxyl group with halogenation agents, then the main product of this step is continuously reacted with amines to produce amides.⁽⁵⁾

As was mentioned above, commonly DEET has been synthesized by activating carboxyl or amine group firstly before using it to react with remaining agent. For the ways to activate *m*-toluic acid, chlorinating reagents like SOCl_2 ,^(8,9,10,11) $(\text{COCl})_2$,⁽¹¹⁾ PCl_3 ,⁽¹²⁾ NbCl_5 ,⁽¹³⁾ and 2,2,2-trichloroacetamide⁽¹⁴⁾ have been



reported to be very useful, but still is was lavish use. Of course, the synthesis of DEET could be direct from *m*-toluic acid reacting with diethylamine, however, this process produced a temporary compound that is diethylammonium *m*-toluate which is a salt; because *m*-toluic acid was weak carboxyl reagent, therefore this method required one more step to remove an H₂O by mean of dehydration reaction and it is performed under very hard condition by using very high pressure, temperature and sometimes combined with the presence of catalysts, which often caused the final product has not good appearance (Fig. 1).⁽¹⁵⁾ Many other methods for synthesis of DEET also could be listed such as dehydration of salt to form *m*-toluic acid and diethylamine, the activation of diethylamine before reacting with *m*-toluic acid or using coupling reagents like *N,N'*-Dicyclohexylcarbodiimide (DCC), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1,1'-Carbonyldiimidazole (CDI), etc.,⁽¹⁶⁾ by using diverse starting materials, for example, *m*-methyl-iodobenzene, *m*-methyl-benzonitrile or *m*-methyl-acetophenone.^(8,9,10)

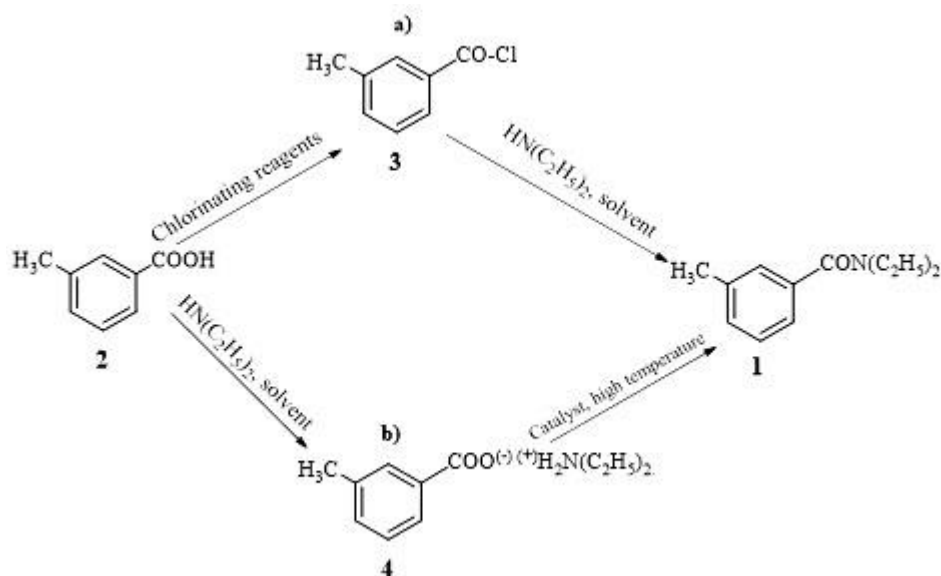


Fig. 1 - Preparation of DEET from *m*-toluic acid and diethylamine.

Summarizing, the process to produce large-scale DEET using the above procedures still has several restrictive points which could be improved to reduce the amount of starting materials, solvents as well



as the byproducts. Accordingly, the most suitable method for synthesis of DEET was performed from *m*-toluic acid, thionyl chloride, and diethylamine, in which two reactions were carried out in single step with one-pot to improve the process and optimize the parameters of this procedure.

In order to introduce the process on an industrial scale, to eliminate the use of toxic chemicals, energy, and preparation time, the objective of this study was to find an optimized method to increase the overall yield of *N,N'*-diethyl-*m*-toluamide synthesis process.

METHODS

To establish suitable reaction conditions, which can apply to industrial scale, the reaction conditions have screened all affected factors on the yield of *N,N*-diethyl-*m*-toluamide.

Effects of reaction parameters on the yield of *N,N*-diethyl-*m*-toluamide. General experiment

Firstly, *m*-toluic acid (compound 2) (1.36 g; 0.01 mol) was added slowly to SOCl_2 (1.5 mL; 0.02 mol) over 15 min with stirring at 15-20 °C, then this reaction mixture was heated to 90 °C for 0.5 h. During the reaction, the progress was monitored by thin layer chromatography (TLC) until the starting material spot completely disappeared in the TLC and found to be completed. Then, the reaction temperature was reduced to 15-20 °C, adding anhydrous ether (20 mL) as solvent. Besides, diethylamine (3.3 mL, 0.03 mol) was prepared by dissolving in anhydrous ether (7 mL) and added to the reaction. After that, the temperature of reaction was increased to 28-30 °C. Then the mixture was cooled to 15-20 °C and pH changed to weakly base condition by using 10% sodium hydroxide (10 mL) with stirring, and removing the aqueous layer to separate the organic phase, and then adjusted it to pH 3-4 with aq.10% HCl (10 mL), then washed two times more with chilling distilled water (2 x 10 mL), dried over anhydrous sodium sulfate and filtered off. Solvent was removed under reduced pressure on a rotary evaporator to dry, and then dried in vacuum desiccator at 20 °C/1 mmHg for 2 h to give 1.7 g DEET (88.77%) as a weak yellow liquid; $R_f = 0.64$ (*n*-hexane: EtOAc, 1: 1, v/v; UV detection of 254 nm).

Effects of chlorinating agents on the yield of DEET

The reaction for preparation of DEET was performed like the same operation as general experiment. Instead of use SOCl_2 , the chlorinating agent was changed to PCl_5 , POCl_3 , $(\text{COCl})_2$, respectively (table 1).



Table 1 - Effect of chlorinating agents on the yield of DEET (1)

No	Chlorinating agents	Boiling point of reaction mixes (degrees)	Stage 1 (minutes)	Stage 2 (minutes)	Compound 1		
					Weight (g)	Yield (%)	Density (g/mL) *
1	SOCl ₂	90	15	30	1.70	88.77	0.9860
2	PCl ₅	180	90	150	1.10	57.70	0.9832
3	POCl ₃	120	150	210	0.96	50.32	0.9770
4	(COCl) ₂	80	30	360	1.22	63.84	0.9814

* Calculated by weighting 1 mL final product at 20 °C.

Reaction parameters: *m*-toluic acid= 0.01 mol; chlorinating agents: SOCl₂, PCl₅, POCl₃, (COCl)₂; molar ratio of (compound 2: chlorinating agents: diethylamine)= (1:2:3).

Conclusion: The reaction chlorinating agent giving the best yield of DEET was SOCl₂ for total reaction time= 45 minutes (the yield 88.77%) (No. 1 in table 1).

Effect of solvent type on the yield of DEET

Experiment: The reaction for preparation of DEET was performed like the same operation as general experiment, chlorinating agent was SOCl₂, and instead of diethyl ether, the solvent type was benzene, *n*-hexane, dichloromethane, ethyl acetate, tetrahydrofuran, acetone, at boiling point (table 2).

Table 2 - Effect of solvent type on the yield of DEET (1)

No.	Solvent	Compound 1		
		Weight (g)	Yield (%)	Density (g/mL) *
1	Diethyl ether	1.70	88.77	0.9820
2	Benzene	1.39	72.75	0.9755
3	<i>n</i> -Hexane	0.68	35.59	0.9730
4	Dichloromethane	1.79	93.67	0.9786
5	Ethyl acetate	1.28	66.99	0.9851
6	Tetrahydrofuran	1.54	80.60	0.9886
7	Acetone	0.72	37.68	0.9757



Reaction parameters: *m*-toluic acid (2)= 0.01 mol; instead of diethyl ether, solvent type was benzene, *n*-hexane, dichloromethane, ethyl acetate, tetrahydrofuran and acetone; molar ratio of compound 2: thionyl chloride: diethylamine= 1:2:3.

Conclusion: The solvent giving the best yield of DEET was dichloromethane (the yield 93.67%) (No. 4 in table 2).

Effect of molar ratio between compound 2 and thionyl chloride on the yield of DEET

Experiment: The reaction preparation of DEET was performed like the same operation as general experiment with dichloromethane as solvent, and molar ratio between thionyl chloride and compound 2 increased from 1.2:1; 1.4:1; 1.8:1; 2.0:1 and 2.2:1, respectively, at 28-30 °C (table 3).

Table 3 - Effect of molar ratio between compound 2 and thionyl chloride on the yield of DEET (1)

No.	Molar ratio of SOCl ₂ : 2	Compound 1		
		Weight (g)	Yield (%)	Density (g/mL) *
1	1.2:1	1.62	84.79	0.9751
2	1.4:1	1.80	94.24	0.9763
3	1.8:1	1.81	94.45	0.9896
4	2.0:1	1.79	93.83	0.9857
5	2.2:1	1.79	93.52	0.9850

Reaction parameters: Solvent was dichloromethane; total reaction time= 45 minutes; molar ratio of diethylamine: (compound 2) = (3:1). Molar ratio between thionyl chloride and compound 2 was 1.2:1; 1.4:1; 1.8:1; 2.0:1; 2.2:1 respectively.

Conclusion: The result found that using molar ratio of thionyl chloride and compound 2 was 1.4:1 which gives the highest yield of DEET (94.24%) (No. 2 in table 3).

Effect of molar ratio between compound 2 and diethylamine on the yield of DEET

Experiment: The reaction for preparation of DEET was performed like the same operation as general experiment, molar ratio between thionyl chloride and compound 2 was 1.4:1, and molar ratio between diethylamine and compound 2 was screened by increasing from 1.5:1; 2.0:1; 2.5:1; 3.0:1 and 3.5:1, respectively (table 4).

**Table 4** - Effect of molar ratio between compound **2** and diethylamine on the yield of DEET (1)

No.	Molar ratio of Diethylamine: 2	Compound 1		
		Weight (g)	Yield (%)	Density (g/mL) *
1	1.5: 1	1.62	84.23	0.9695
2	2.0: 1	1.73	90.46	0.9776
3	2.5: 1	1.81	94.54	0.9818
4	3.0: 1	1.80	94.24	0.9718
5	3.5: 1	1.81	94.51	0.9823

Reaction parameters: Solvent was dichloromethane; total reaction time= 45 minutes; molar ratio of SOCl_2 (compound **2**)= (1.4:1), and molar ratio of diethylamine (compound **2**) from 1.5:1 to 3.5:1, respectively.

Conclusion: The result found that using molar ratio of diethylamine and compound **2** was 2.5:1 giving the highest yield (94.54%) (No. 3 in table 4).

Final results: The combination of reaction parameters found that the highest yield of DEET were the following: *m*-toluic acid= 0.01 mol; reaction condition: reaction temperature: 28-30 °C; reaction time= 60 minutes; molar ratio of compound (2): SOCl_2 : diethylamine= 1:1.4: 2.5; yield = 94.54%.

RESULTS

In this report, starting materials *m*-toluic acid, thionyl chloride, and diethylamine were chosen for the synthesis of DEET because of high yield reaction; and also, they are very low cost (Fig. 2). Besides, two reactions were performed within one-pot via highly active intermediate compound *m*-toluoyl chloride, following the conversion of *m*-toluoyl chloride into DEET with a mixture of diethylamine and dichloromethane at boiling temperature of dichloromethane (around 40°C).

Especially, all by-products were highly water-soluble, and could easily be removed with liquid-liquid extraction method (water-dichloromethane). Therefore, the work-up step only used the liquid-liquid



extraction to purify the final compound.

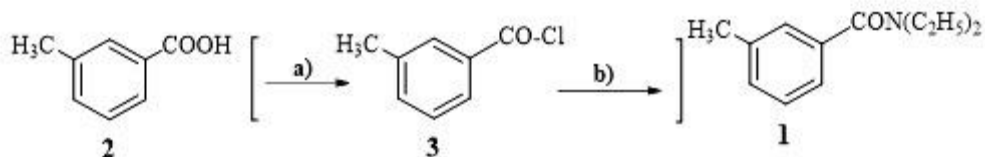


Fig. 2 - Preparation of DEET from *m*-toluic acid and diethylamine via *m*-toluoyl chloride in single step.

Reagents and conditions: a) SOCl₂/90°C/0.5 h; b) HN(C₂H₅)₂/CH₂Cl₂/28-30°C/1.0 h; overall yield: 98%. Briefly, *m*-toluic acid (1 equiv.) was reacted with thionyl chloride (1.4 equiv.) and stirred at 28-30°C over 10 min, and heated to 90°C for 0.5 h, then reaction mass was cooled to room temperature, then 0.5 L dichloromethane was added with stirring for over 10 min, then a mixture of diethylamine (2.5 equiv.), and dichloromethane (0.3 L) was added and stirred at 28-30°C for 1.0 h. Next step was only reduction of the temperature to room temperature, and the following process was to change pH: firstly, the reaction was adjusted to pH 8-9 with 10% sodium hydroxide with stirring. Then the organic layer was acidified again to pH 3-4 using 10% aq. HCl; finally, the organic layer was washed with chilling distilled water and dried by anhydrous sodium sulfate. The solvent was evaporated and exhausted under vacuum (1 mmHg) at 20-25 °C to give a yield of DEET of 96-98%.

Scale-up of synthetic process of *N,N*-diethyl-*m*-toluamide (DEET)

At 15-20 °C, *m*-toluic acid (340.5 g; 2.5 mol) was added slowly to SOCl₂ (250 mL; 3.5 mol), over 30 min with stirring, then this reaction mixture was heated to 90°C for 0.5 h, checked by TLC until the starting material spot (compound 2) disappeared completely; then reaction was done. After the reaction was finished, the temperature was cooled down to 15-20 °C, dichloromethane (1 250 mL) was added, and then diethylamine (650 mL, 6.25 mol) was diluted in dichloromethane (750 mL). The temperature was heated again to 28-30°C, until *m*-toluoyl chloride spot completely disappeared in the TLC (1 h). The reaction temperature was cooled to room temperature by adding dichloromethane (1 750 mL) and distilled water (1 250 mL).

As general experiment, the mixture was treated by adjusting to pH 8-9 with aqueous solution of 10%



sodium hydroxide (1 250 mL). The organic layer was separated and acidified again to pH 3-4 using 10% HCl (1 375 mL). The dichloromethane phase was separated and washed with chilling distilled water two times more (2 x 750 mL) and dried by anhydrous sodium sulfate; the solvent was distilled under reduced pressure on a rotary evaporator at 20-25 °C to dry it, and then kept to dry in vacuum desiccators at 20 °C/1 mmHg for 2 h to give 470.3 g DEET (98.35%), as a weak yellow liquid; $d = 0.9999 \text{ g/mL}$ (20 °C), $R_f = 0.64$ (*n*-hexane: EtOAc = 1:1, v/v; UV detection of 254 nm); purity (HPLC): 97.2%; infrared (IR) (KBr), ν_{max} , cm^{-1} : 2971-2874 (C-H), 1625 (C=O), 1 215 (C-N); mass spectroscopy (MS) (m/z): 191.8 $[\text{M}+\text{H}]^+$; 118.8 $\text{M}-[\text{N}(\text{C}_2\text{H}_5)_2]^+$; nuclear magnetic resonance spectroscopy ($^1\text{H-NMR}$) (500 MHz-DMSO-*d*6), δ (ppm): 7.29 (t, 1H, $J = 10 \text{ Hz}$); 7.21 (d, 1H, $J = 7.5 \text{ Hz}$); 7.14 (s, 1H); 7.11 (d, 1H, $J = 7 \text{ Hz}$); 3.42 (s, br, 2H); 3.17 (s, br, 2H); 1.12 (s, br, 3H); 1.04 (s, br, 3H); $^{13}\text{C-NMR}$ (125 MHz, DMSO-*d*6), δ (ppm): 170.0 (C=O); 137.7 (ArC-3); 137.3 (ArC-1); 129.5 (ArC-4); 128.2 (ArC-5); 126.5 (ArC-2); 123.0 (ArC-6); 42.7 (CH_2); 38.5 (CH_2); 20.8 Ar- CH_3 ; 14.0 (CH_3); 12.8 (CH_3).

DISCUSSION

During the synthetic procedure, the use of chlorinating toxic reagents was optimized to more reasonable level; the synthesis of *m*-toluic acid to DEET via intermediate *m*-toluoyl chloride was carried out within one step with thionyl chloride, decreasing the separation and purification of intermediate *m*-toluoyl chloride step. And also, the reaction between *m*-toluoyl chloride and diethylamine was completed under mild condition without the use of acid binding agent. Besides, the type of solvents also was screened to avoid highly flammable or carcinogenic solvent, and there was no need to use any catalyst.

Especially, during the reaction of the synthesis one-pot of DEET, all side products were easily removed during the work-up step with the liquid-liquid extraction method to obtained DEET product at high purity, and also discarded the separation and purification of DEET (1) step by using vacuum distillation or column chromatography, as previous research, which led to decrease the total time of process, and enhanced the overall yield of procedure of DEET preparation. All parameters of reaction were affected on the yield of DEET as the method for execution of reaction, the type of chlorinating agents (table 1), solvent use in reaction (table 2), the molar ratio of reagents (table 3 and table 4), the method to carry out



the reaction mixture, the method for isolation and purification of DEET, were totally examined and optimized.

The overall yield is very high (96-98%) and high purity (HPLC): 95,5-97.6%; g). The total preparation time of DEET from *m*-toluic acid was shortened (5-6 h compared with 12-24 h in previous work).

An improved procedure for the synthesis of *N,N*-diethyl-*m*-toluamide (DEET) or *N,N*-diethyl-*m*-methylbenzamide is established where the use of all reagents was optimized in suitable amount to apply in industrial production.

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Conflict of interest

No conflicts of interest are indicated.

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