Technology Presentation

**A new method for synthesis of *N,N*-diethyl-*m*-methylbenzamide**

Nuevo método para la síntesis de *N,N*-dietil-*m*-metilbenzamida

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**ABSTRACT**

**Introduction:** N, N-diethyl-m-methylbenzamide or N, N-diethyl-m-toluamide (DEET), is well known as an insect repellent. In addition, it is used to improve the dermal and transdermal delivery of many drugs.

**Objectives:** To present a feasible procedure to synthesize DEET from m-toluic acid and diethylamine.

**Methods:** The m-toluic acid was activated with 1,1'-carbonyl-diimidazole, to obtain the intermediate product 1- (m-toluoyl) imidazole that continues to react with diethylamine, to produce DEET. In this way, the factors affecting the synthesis of N, N-diethyl-m-toluamide are improved.

**Results:** DEET was obtained through an optimal procedure. The by-products of the reaction are soluble in water; they are easily removed by the liquid-liquid extraction method with water and dichloromethane. Most of the DEET obtained has high purity. The yields were 94 to 95 %.

**Conclusions:** An improved route has been provided for a simple and efficient synthesis of DEET from m-toluic acid and diethylamine in the presence of 1,1'-carbonyl-diimidazole. The synthesis procedure was carried out in one-pot, and the isolation of DEET was achieved by liquid-liquid extraction. The total procedure time was significantly reduced. This synthesis method is easily scalable and industrially feasible.

**Keyword:** *m*-Toluic acid; *N,N*-diethyl-*m*-toluamide; ingredient, insects repellent.

**RESUMEN**

**Introducción:** La N,N-dietil-m-metilbenzamida o N,N-dietil-m-toluamida (DEET), es muy conocida como repelente de insectos. Además, se utiliza para mejorar la administración dérmica y transdérmica de muchos fármacos.

**Objetivos:** Presentar un procedimiento factible para sintetizar DEET a partir de ácido m-toluico y dietilamina.

**Métodos:** El ácido m-toluico fue activado con 1,1’-carbonil-diimidazol, para obtener el producto intermedio 1- (m-toluoil) imidazol que continúa reaccionando con dietilamina, para producir DEET. De este modo, se mejoran los factores que afectan la síntesis de N, N-dietil-m-toluamida.

**Resultados:** Se obtuvo DEET mediante un procedimiento óptimo. Los subproductos de la reacción son solubles en agua; se eliminan fácilmente mediante el método de extracción líquido-líquido con agua y diclorometano. La mayor parte del DEET obtenido tiene gran pureza. Los rendimientos fueron del 94 al 95 %.

**Conclusiones:** Se ha proporcionado una ruta mejorada para una síntesis simple y eficaz de DEET a partir de ácido m-toluico y dietilamina en presencia de 1,1'-carbonil-diimidazol. El procedimiento de síntesis se realizó en un solo reactor y el aislamiento de DEET se logró mediante extracción líquido-líquido. El tiempo total de procedimiento se redujo significativamente. Este método de síntesis es fácilmente escalable y factible industrialmente.

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

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**INTRODUCTION**

*N,N*-diethyl-*m*-methylbenzamide or *N,N*-diethyl-*m*-toluamide (DEET)(**1**) was synthesized in 1944 and used in army as insect repellent.(1) Until now, DEET became the most popular reagent for insect repellent because of its effects in preventing insect attacks which causes many fatal diseases such as Malaria, Zika, viral hemorrhagic fever, etc.

Thus far, DEET could be synthesized by many methods. Among them, the most common is the acylation of diethylamine with *m*-toluic acid deriving its halogenation with thionyl chloride, oxalyl chloride or phosphorus chloride.

Numerous papers and patents regarding synthetic method of *N,N*-diethyl *m*-methylbenzamide (**1**) started from various input materials such as *m*-toluic acid, *m*-toluoyl chloride, butyl *m*-toluoate, *m*-toluyl-nitrile, *m*-xylene, etc. with diethylamine.

The essential nature of reaction for preparationof *N,N*-diethyl-*m*-methylbenzamide (**1**) from *m*-toluic acid derivatives and diethylamine is *m*-toluoylation, the link H-N of diethylamine. However, the *m-*toluic acid (**2**) is a weak *m*-toluoylation agent, therefore cannot easily derivate m-toluoylated diethylamine into *N,N*-diethyl-*m*-methylbenzamide. This process creates diethylammonium *m*-toluolate, the salt of diethylamine and *m*-toluic acid. DEET could be synthesized by dehydration of that salt under strict conditions,(2,3,4,5) such as in the presence of expensive catalysts and high temperature and/or pressure, that causes dark color of DEET product, which require other step to purify it using vacuum distillation or column chromatography (Fig. 1).

To replace the above process, *m*-toluic acid often is activated into *m*-toluoyl chloride (**3**) by chlorinating agents. The most common method for synthesis of DEET is acylation of diethylamine with *m-*toluic acid (**2**) or *m*-toluoyl chloride (**3**),(6,7) prepared from m-toluic acid and a chlorinating agents,(8,9,10,11,12,13,14) such as thionyl chloride,(8,9,10,11) oxalyl chloride,(10) phosphorus trichloride,(12) niobium pentachloride,(13) 2,2,2-trichloro-acetamide,(14) that are highly toxic reagents (Fig. 2).

Nonetheless, above listed methods for preparation of DEET have a number of common deficiencies, such as the synthesis of **1** from *m*-toluic acid and diethylamine via intermediate *m-*toluoyl chloride (**3**), which was prepared from *m*-toluic acid by treatment with chlorinating agents that are highly toxic reagents, while dehydration of compound **4** into **1** must be carried out at conditions of high temperature; and finally the purification of **1** must use vacuum distillation or column chromatography. Besides, the total preparation time of that processes is long. and also lead to lower economic yield. Therefore, the above procedures are feasible for industrial scale.



**Fig. 1 -** Preparation of DEET by dehydration of diethylammonium *m*-toluate (**4**).(2,3,4,5)

Reagents and conditions:

a) Chlorinating reagents, solvent;

b) HN(C2H5)2, solvent;

c) Vacuum distillation or column chromatography.



**Fig. 2 -** Preparation of DEET by acylation of diethylamine with the m-toluyl chloride.(8,9,10,11,12,13,14)

Reagents and conditions:

a) HN(C2H5)2, solvent;

b) Solvent, high temperature, catalyst;

c) Vacuum distillation or column chromatography.

Accordingly, we have chosen this method as a new and feasible method for synthesis of DEET (Fig. 3). Besides, the parameters of this procedure were optimized to produce the best condition. Our goal was to increase the effectiveness of the procedure, carrying it out at low temperature in one-pot, with relative higher overall yield and limited use of toxic reagents and solvents, as well as no necessary purification by vacuum distillation or column chromatography.



**Fig. 3 -** Method for synthesis of DEET from compound 2 and diethylamine using the coupling agent CDI.

Reagents and conditions:

a) CDI/4-DMAP/CH2Cl2 and;

b) HN(C2H5)2

**METHODS**

We have tried to screen all factors affecting the yield of *N,N*-diethyl-*m*-toluamide, to establish the suitable reaction conditions which can apply to laboratory scale.

**1. Effect of solvent types on the yield of (1):**

Solution of *m*-toluic acid (**2**) (1.36 g, 0.01 mol), 1,1’-carbonyl-diimidazole (1.62 g, 0.01 mol) and 4-dimethylamino-pyridine (0.037 g, 0.0003 mol) in dried dichloromethane (5 mL) was stirred at room temperature, then heated to 35-40 oC and to reflux until the compound **2** completely disappeared (for 0.5 hour; indicated by thin layer chromatography (TLC)); solvents: *n*-hexane: C2H5OAc, ratio 1:1 volume/volume (v/v); visualization: UV lamp of 254 nm). Then diethylamine (3.1 mL, 0.03 mol) was added and the mixture heated to 35-40 oC until the compound **7** completely disappeared (1 h, the reaction was monitored by TLC, *n*-hexane: EtOAc = 1:1, v/v; detection by UV of 254 nm).

After the reaction completion, the mixture was cooled to 15-20 oC and to this mixture, dichloromethane (5 mL) was added and adjusted to pH 9-10 with 5 % sodium hydroxide (3 mL) with stirring. The dichloromethane layer was separated and washed with cooled water; the organic layer was adjusted to pH 5-6 with aq. 10 % HCl (7 mL). The dichloromethane was separated and washed with distilled cold water (8 mL x 2). The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum at 35-40 oC and dried under vacuum at 20oC/1 mmHg for 2 h to give 1.6996 g DEET (**1**) (88.86 %), as a slight yellow liquid; purity (HPLC): 95-97%.

The reaction preparation of (**1**) was performed with the same above operation*,* but instead solvent type were diethyl ether, *n*-hexane, dichloromethane and ethyl acetate (table 1).

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

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Reaction parameters: *m*-toluic acid (**2**) = 0.01 mol; solvent type, instead of diethyl ether, *n*-hexane, dichloromethane, ethyl acetate; molar ratio (compound **1**: CDI: diethylamine) = (1:1:3). Density (g/mL)\* was calculated by weighting 1 mL final product at 20 oC.

Conclusion: The solvent that gives the best yield of **1** was dichloromethane (yield 88.86 %) (No. 3 in table 1).

**2. Effect of** **molar ratio between compound 2 and CDI on the yield of compound (1):**

Experiment: The reaction preparation of **1** was performed with the same operation as investigation on the effect of solvent type on the yield of **1**, but solvent was dichloromethane; molar ratio between compound **2** and CDI was 1:1.0; 1:1.1; 1:1.2; 1:1.3 and 1:1.4, respectively (table 2).

**Table 2 -** Effect of molar ratio between compound **2** and CDI on the yield of DEET

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Reaction parameters: Solvent was dichloromethane; total reaction time = 90 minutes; molar ratio of (compound **2**: diethylamine) = (1:3). Molar ratio between compound **2** and CDI was 1:1.0; to 1:1.4, respectively.

Conclusion: The results found that using molar ratio of compound **2** and CDI 1:1.2 got the highest yield of **1**, 93.68 % (No. 3 in table 2).

**3. Effect of molar ratio between compound 2 and diethylamine on the yield of 1:**

Experiment: The reaction preparation of **1** was performed with the same operation as investigation on the effect of molar ratio between compound **2** and CDI on the yield of **1**,but molar ratio between compound **2** and CDI was 1:1.3, and molar ratio between compound **2** and diethylamine was 1:1.5; 1:2.0; 1:2.5; 1:3.0 and 1:3.5, respectively (table 3).

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



Reaction parameters: Solvent was dichloromethane; total reaction time = 90 minutes; molar ratio of (compound **2**: CDI) = (1:1.2), and molar ratio of (compound **2**: diethylamine) from 1:1.5 to 1:3.5, respectively.

Conclusion:The result found that using molar ratio of compound **2** and diethylamine 1:2.0 got the highest yield, 94.03 % (No. 2 in table 3).

The combination of reaction parameters found that the highest yield of DEET (**1**) were the following: *m*-toluic acid (**2**) = 0.01 mol; reaction condition: total reaction time = 90 minutes; molar ratio of (compound **2**: CDI: diethylamine) = (1:1.2:2.0); yield = 94.03 %.

**RESULTS**

Based on the optimal conditions, we have applied and scaled to synthesize the final compound (DEET).

A solution of *m*-toluic acid (**2**) (340.39 g, 2.5 mol), 1,1’-carbonyl-diimidazole (486.46 g, 3.0 mol) and 4-dimethylamino-pyridine (9.16 g, 0.075 mol) in dried dichloromethane (1250 mL) was stirred at room temperature and then heated to 35-40 oC to reflux, until the compound **(2)** completely disappeared (for 0.5 h, indicated by TLC, solvents: *n*-hexane: C2H5OAc = 1: 1, v/v; visualization: UV lamp of 254 nm), then diethylamine (520 mL, 5.0 mol) was added and heated to 35-40 oC until the intermediate compound **7** completely disappeared using TLC to follow.

After the completion of reaction, the mixture was cooled to 15-20 oC and mixed with dichloromethane (1250 mL), then adjusted to pH 9-10 with 5 % sodium hydroxide (750 mL) with stirring. The dichloromethane layer was separated and washed with cold water; the organic layer was adjusted to pH 5-6 with aq. 10 % HCl (1750 mL). The dichloromethane was separated and washed with distilled cold water (2000 mL x 2). The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum at 35-40 oC and dried under vacuum at 20 oC/1 mmHg for 2 h, to give 457.53 g DEET (**1**) (95.68 %), as a weak yellow liquid.

Analytical data: The purity of final product was checked using high-performance liquid chromatography (HPLC) system: 95-97 %; Infrared spectroscopy (IR) (KBr, νcm-1): 2970-2873 (C-H), 1625 (C= O), 1215 (C-N). Mass spectroscopy (MS): found 191.8 [M], calculated: 191.27. Nuclear magnetic resonance (NMR) data using solvent dimethyl sulfoxide deuteride (DMSO-*d6*):(1) H-NMR (500MHz, DMSO-*d6*) δ (ppm) 7.29 (triplet, 1H, ArH, J = 10 Hz), 7.22 (doublet, 1H, ArH, J = 5Hz), 7.13 (singlet, 1H, ArH), 7.11 (doublet, 1H, ArH, J = 7 Hz) 3.42 (singlet, broad, 2H, CH2), 3.17 (singlet, broad, 2H, CH2), 2.32 (singlet, 3H, CH3-Ar), 1.12 (singlet, broad, 3H, CH3) 1.04 (singlet, broad, 3H, CH3).(13) C-NMR (125MHz, DMSO-*d6*) δ (ppm) 169.96 (C=O), 137.6 (C3-Ar), 137.3 (C1-Ar), 129.4 (C4-Ar), 128.1 (C5-Ar), 126.5 (C2-Ar), 122.9 (C6-Ar) 42.7 (CH2), 38.56 (CH2), 20.8 (CH3-Ar), 13.9 (CH3-CH2), 12.7 (CH3-CH2).

**DISCUSSION**

We demonstrate that (Fig. 3) **1** can be synthesized from *m-*toluic acid (**2**) and diethylamine, in the presence of 1,1’-carbonyl-diimidazole (**5**) and 4-dimethylaminopyridine (4-DMAP (**6**)) in dichloromethane. With two reactions in one-pot via high activity of intermediate compound1-(*m*-toluoyl) imidazole (**7**)which did not require the separation and purification. Especially in this study, all byproducts were water-soluble, easily removed in aqueous workup with the liquid-liquid extraction method (water-dichloromethane). Most of DEET obtained was of exceptional purity, therefore was not necessary to purify it by vacuum distillation or column chromatography, as reported earlier.

The procedure for preparation of DEET from *m-*toluic acid (**2**), 1,1’-carbonyl-diimidazole CDI, **5** in the presence of 4-DMAP (**6**) as catalyst via intermediate 1-(m-toluoyl) imidazole (**7**) and diethylamine has shown in figure 4.



**Fig. 4 -** Synthesis of DEET from m-toluic acid and diethylamine with 1,1’-carbonyl-diimidazole.

The 4-DMAP catalyzed acylation of diethylamine by 1-(*m*-toluoyl) imidazole (R-CO-I, I: imidazole is currently believed to proceed via the nucleophilic catalysis mechanism, shown in figure 5. This mechanism is supported by following observations:



**Fig. 5 -** Nucleophilic mechanism for amidation of *m*-toluic acid and diethylamine catalyzed by 4-DMAP.

The above synthesis procedure has the following advantages:

a) Highly toxic reagents and solvents were not used;

b) The conversion of **2** to **1** via intermediate 1-(*m*-toluyl) imidazole (**7**)wascarried out at low temperature (35-40 oC);

c) The separation and purification of the intermediate **7** was not necessary, it led to a decrease in the total time of the process and increased the overall performance of the DEET preparation process;

d) The separation and purification of DEET by vacuum distillation or column chromatography was not necessary, and was found that one-pot synthesis of DEET was operationally straight, and with all byproducts easily removed in aqueous workup with the liquid-liquid extraction method (water-dichloromethane);

e) The parameters of reaction as the method for execution of reaction, the reaction temperature, the reaction time, the molar ratio of reagents, the solvents type, solvent volume, the method for execution of reaction, the method for isolation, purification of product **1** was also examined (as shown in table 1, table 2 and table 3);

f) Total preparation time of **1** from **2** was shorter. As a result, we have set up the new, feasible method for synthesis of *N,N*-diethyl *m*-methyl-benzamide (**1**) with more advantages than the previous reported, including simplicity of synthesis procedure; high synthesis yield 94-95 % compared with 51-85 % in previous publications.

BIBLIOGRAPHIC **REFERENCES**

1. Kitchen LW, Lawrence KL, Coleman RE. The role of the United States military in the development of vector control products, including insect repellents, insecticides, and bed nets, J. Vector. Ecol. 2009

[access: 18/12/2019] 34: 50-61. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1948-7134.2009.00007.x>

2. Zhu Y, Wang X, inventor. Cangzhou Panshi Chemical Co., Ltd. Method for continuous water removal production of amide product. Chinese Patent CN 104418760. 2015 Mar 18. Available from: <https://patents.google.com/patent/CN104418760A/en?oq=CN+104418760>

3. Warren J, Westphal D, Zoubek S. Pfizer Inc. Process for the production of amides. Wipo Patent WO 2002036559. 2002 Sep 6. Available from: <https://patents.google.com/patent/WO2002036559A3/en?oq=WO+2002036559>

4. Khalafi-Nezhad A, Parhami A, Soltani R, Navid M, Zarea A. Efficient method for the direct preparation of amides from carboxylic acids using tosyl chloride under solvent-free conditions, Tetrahedron Letters. 2005 [access: 10/03/2020]; 46(40): 6879-82. Available from:

<https://www.sciencedirect.com/science/article/abs/pii/S0040403905017399>

5. Krull M, Morschhaeuser R, Lerch A, Ritter H, Schmitz S. Clariant International Ltd. Process for the preparation of tertiary amides of alkylphenylcarboxylic acids. Germany Patent DE 102006047620. 2008 Nov 27. Available from: <https://patents.google.com/patent/DE102006047620B4/en?oq=DE+102006047620>

6. Zhang F. Tianjin Chemical Reagent Research Institute. Method for preparing of N,N-diethyl-m-methylbenzoyl amide, Chinese Patent CN 101,914,034. 2010 Dec 15. Available from:

<https://patents.google.com/patent/CN101914034A/en?oq=CN+101%2c914%2c034>

7. Croud VB, Maltas PJ, McCallien DWJ. Johnson Matthey Public Limited Company. Identifiable chemical product, Wipo Patent WO 2016185177. 2016 Nov 24. Available from:

<https://patents.google.com/patent/WO2016185177A1/en?oq=WO+2016185177>

8. Peter KH, Edward G, Neeland. A Modified Synthesis of Insect Repellent DEET. Journal of Chemical Education. 1998 [access: 22/12/2019]; 75(10): 1267-1268. Available from:

<https://pubs.acs.org/doi/10.1021/ed075p1267>

9. Zhuang Z, Zhi-Peng H, Liao, Wei-Wei. Asymmetric Synthesis of Functionalized Dihydronaphthoquinones Containing Quaternary Carbon Centers via a Metal-Free Catalytic Intramolecular Acylcyanation of Activated Alkenes. Organic Letters. 2014 [access: 08/01/2020]; 16(12): 3380-3. Available from: <https://pubs.acs.org/doi/abs/10.1021/ol501427h>

10. Habeck JC, Diop L, Dickman M. Synthesis of N,N-Diethyl-3-methylbenzamide (DEET): Two Ways to the Same Goal. Journal of Chemical Education. 2010 [access: 03/03/2020]; 87(5): 528-9. Available from: <https://pubs.acs.org/doi/10.1021/ed800169h>

11. Xie S, Lin H, Liu D, Shi C, Li L, Shen B, Zhang L. Guangzhou Liby Enterprise Group Co Ltd. A kind of mite-assistant fabricses care composition. Chinese Patent CN 104988725. 2015 Oct 21. Available from: <https://patents.google.com/patent/CN104988725B/en?oq=CN+104988725>

12. Ellis LC, Kise MA. Virginia Chemicals Inc. Process for the manufacture of *N,N*-diethyl-m-toluamide by aqueous caustic procedure. United State Patent US 3,870,756. 1975 Mar 11. Available from: <https://patents.google.com/patent/US3870756A/en>

13. Nery MS, Ribeiro RP, Lopes CC, Lopes RSC. Niobium pentachloride promoted conversion of carboxylic acids to carboxamides: Synthesis of the 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloid structures. Synthesis. 2003 [access: 05/03/2020]; 2: 272-6. Available from: <https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2003-36823>

14. Chaysripongkul S, Pluempanupat W, Jang DO, Chavasiri W. Application of Cl3CCONH2/PPh3 towards the synthesis of bioactive amides. Bulletin of the Korean Chemical Society. 2009 [access: 08/03/2020]; 30(9): 2066-70. Available from:

<http://koreascience.or.kr/article/JAKO200902727494345.page>

**Conflict of interest**

No conflicts of interest are indicated.

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