

Short Note

N,N-Diethyl-3-methylbenzamide

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Abstract: The development of new techniques for the preparation of organic compounds is important, with catalytic processes being key to this innovation. The development of copper-based metal-organic frameworks to promote oxidative couplings has allowed the synthesis of amides in a very effective manner. This methodology has been successfully applied to the unique preparation of the bioactive compound *N,N*-diethyl-3-methylbenzamide, with excellent performance (>99% conversion and 95% yield of pure isolated product) on a preparative scale. The described procedure can be classified as an excellent synthesis (EcoScale) considering environmental and economic factors based on different “green metrics” (atom economy, reaction mass efficiency, materials recovery factor, stoichiometric factor, E-factor).

Keywords: amide; copper; heterogeneous catalysis; metal-organic framework; oxidative coupling

1. Introduction

Amides are an essential structural unit in organic compounds with applications in pharmaceuticals, agrochemicals, and polymers [1]. This type of bond is formed by the condensation reaction of an acid and an amine. Experimentally, the reaction presents difficulties due to the acid–base reaction between the components, so it is necessary to use more energetic conditions. Alternatively, coupling reagents or activators can be used to facilitate the transformation, although this usually involves additional reaction steps [2,3]. In addition, oxidative couplings have proved to be an interesting alternative in carbon-nitrogen bond formation [4,5]. Thus, amides can be synthesized by coupling aldehydes or alcohols with amines or formamides, and in a less-studied approach carboxylic acids can be coupled with formamides. For the latter, several copper catalysts have been reported in the coupling of benzoic acids with *N,N*-dimethylformamide (DMF) and *N,N*-diethylformamide (DEF), both homogeneous (i.e., CuCl₂ [6], Cu(OTf)₂ [7], Cu(ClO₄)₂·6H₂O [8]) and heterogeneous (i.e., CuO nanoparticles [9], Fe₂O₃@SiO₂-Cu(acac)₂ nanoparticles [10]). In addition, CuCl₂ has been tested with other formamides, although the need for a chlorinated solvent (such as 1,2-dichloroethane) is a drawback of this CuCl₂-catalyzed coupling. In all the cases, the presence of an oxidant is necessary, *tert*-butyl hydroperoxide and di-*tert*-butyl peroxide being mainly employed. In the search for catalytic systems for oxidative coupling, the metal-organic framework based on copper and 1,3-bis(carboxymethyl)imidazole (**bcimim**) linkers has shown the ability to promote the activation of *tert*-butyl hydroperoxide for the coupling of formamides with carboxylic acids with good yields and selectivity. The catalyst is very robust for a wide variety of carboxylic acid (both aromatic and aliphatic) and formamides [11].

N,N-Diethyl-3-toluamide (DEET) is a highly effective anti-mosquito agent [12]. It was developed for military use by the Department of Agriculture of the United States of America during World War II [13]. Despite being introduced more than 60 years ago, it is still widely used in mosquito repellents [14]. Therefore, the resulting synthesis of this product is attractive, being of high synthetic value in the application of new strategies, especially with robust and recyclable heterogeneous catalysts. Particularly, the reaction of



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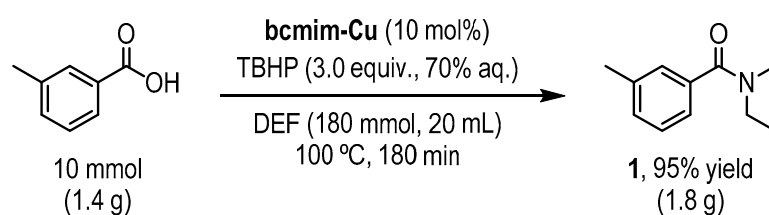
3-toluic acid and DEF has been promoted with propyl phosphonic anhydride (T3P®) and HCl, forming the expected DEET in 91% yield [15].

2. Results and Discussion

The catalyst employed for the oxidative coupling is a metal-organic framework (MOF) **bcmim-Cu**, which is straightforwardly prepared from copper acetate and the linker 1,3-bis(carboxymethyl)imidazole (**bcmim**). The synthesis of **bcmim** was carried out from glycine, glyoxal, and formaldehyde using water as the solvent, giving the corresponding zwitterion as a white solid [16]. The robust synthesis is scalable to multigram with easy and convenient isolation, which represents a methodology with a low environmental impact having an E-factor of 4.4. Next, the ligand **bcmim** and copper(II) acetate were dissolved in water, at room temperature, and then methanol was added to cause the precipitation of MOF **bcmim-Cu** as a blue powder [11].

The protocol developed for the oxidative coupling of acids and formamides catalyzed by **bcmim-Cu** has proved to be effective, with the slow addition of the oxidant (TBHP) and the amount of formamide (18 equivalents) being key factors for the reaction to proceed successfully [11]. The reaction does not need any additional solvent to be carried out, with the formamide as the reagent, and the reaction media. Excess formamide can be easily recovered after a distillation process, if necessary. Remarkably, it has been described that the catalyst can be separated (by centrifugation) and treated with water and methanol to maintain its activity and morphology, up to 5 cycles, having not been tested further [11].

At this point, it is of interest to apply the methodology for the preparation of DEET. Following the standard conditions (100 °C, 100 min), 3-toluic acid (1 mmol) was combined with *N,N*-diethylformamide (18 mmol) to afford exclusively the desired product in 92% conversion, although part of the product was lost during the purification process by column chromatography (66% yield). Noteworthy, DEET was exclusively formed during the reaction, and the *N*-mono-dealkylated byproduct was not observed as previously reported during the preparation of *N,N*-diethyl amides by oxidative coupling [11]. Next, the reaction time was extended to 3 h to improve the synthesis on a larger scale (using 1.4 g of 3-toluic acid), achieving full conversion with the exclusive formation of DEET (Scheme 1). Moreover, the product was isolated in 95% yield by recovering the excess formamide by distillation and filtering the residue through a pad of silica gel, without the need for any further purification. The performance of the reaction is better on a preparative scale than on a low scale.



Scheme 1. Synthesis of *N,N*-diethyl-3-toluamide in gram scale.

Concerning the pure compound, the IR spectrum shows a characteristic band at 1628 cm^{-1} corresponding to the carbonyl bond (C=O, st.) of *N,N*-disubstituted amide. The $^1\text{H-NMR}$ spectrum shows different signals for the two ethyl groups due to the restricted rotation of the amide group at moderate temperatures, making the molecular environment different (Supplementary Materials). Thus, the methylene groups appear at 3.53 and 3.26 ppm, and the methyl groups in the interval 1.34–0.98 ppm; the signals are broad without defined multiplicity due to the restricted rotation.

Following, different metrics have been analyzed to develop an understanding of the environmental impact of the synthesis of DEET by the **bcmim-Cu** catalyzed oxidative coupling. The EcoScale, reported by Van Aken, represents an analytic tool to evaluate an organic synthesis, the value of this semiquantitative scale being calculated as 100 minus a range of penalty points based on the yield, cost of the materials, safety reaction conditions,

and ease of work-up/purification [16]. The protocol herein described for the synthesis of DEET provides a high purity product with a score of 76 in the EcoScale (Table 1), being qualified as an excellent preparation on this scale [17]. In addition, other parameters such as atom economy (AE), stoichiometric factor (SF), reaction mass efficiency (RME), materials recovery parameter (MRP), reaction yield, and environmental factor profile (E-factor referring to kernel, excess, solvent, catalyst, work-up, and purification) have been calculated (Table 1) [18]. The E-factor of the transformation is 21.13, although an analysis of the profile of the environmental factor shows that the main waste sources are the excess of the reagents and the purification process (Table 1 and Figure 1a). However, the excess formamide and the catalyst, which are half of the waste (Figure 1a) can be easily recovered by distillation and centrifugation (or filtration), respectively. Consequently, the main waste of this procedure is the purification process (46% of the E-factor). The analysis of other parameters, which have been defined by Andraos [18], shows that the reaction has low RME (7.6%) and 1/SF (14.7%) due to the excess of reagents employed in the reaction, but as these potential drawbacks are mitigated by the possibility of material recovery, the value for MRP is 93.4% (Table 1, Figure 1b).

Table 1. Green metrics for the synthesis of DEET by oxidative coupling catalyzed with **bcmim-Cu**.

Parameter	Value	(%) ¹
Reaction yield (Rxn yield)		95.3
Atom economy (AE)	0.584	58.4
Stoichiometric factor (SF)	6.81	
1/SF	0.147	14.7
Reaction mass efficiency (RME)	0.076	7.6
Materials recovery parameter (MRP)	0.934	93.4
E-factor (total)	21.13	
E-factor (kernel)	0.80	
E-factor (excess)	10.44	
E-factor (catalyst)	0.24	
E-factor (solvent)	0.00	
E-factor (work-up)	0.00	
E-factor (purification)	9.65	
EcoScale	76	

¹ Some parameters can be expressed as a percentage.

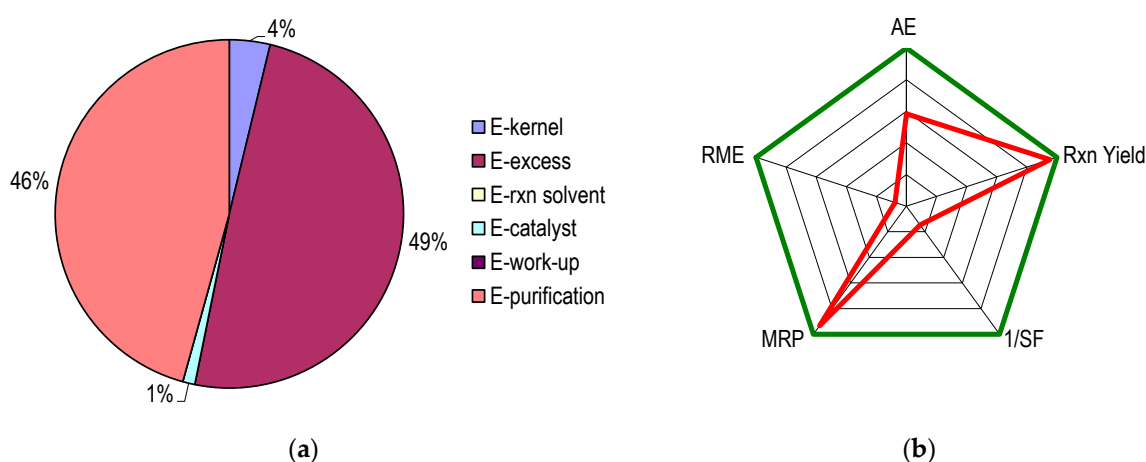
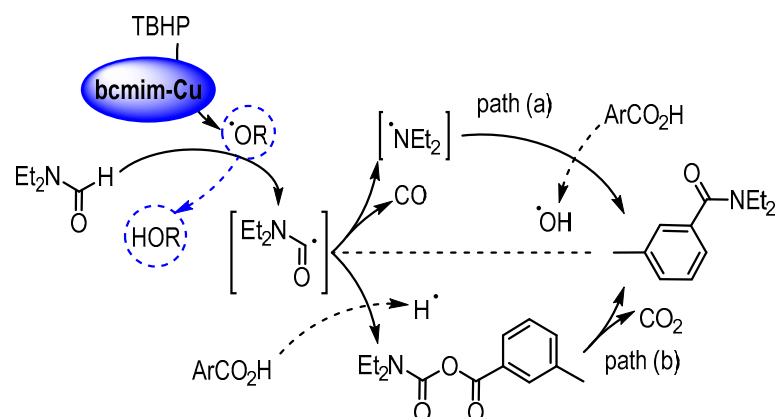


Figure 1. (a) E-factor profile; (b) radial-pentagon diagram with metrics (%): reaction yield, atom economy (AE), reaction mass efficiency (RME), materials recovery parameter (MRP), inverse of stoichiometric factor (1/SF).

Regarding the mechanism, it has been previously reported that radicals are involved in as intermediates [11]. A possible mechanism (Scheme 2) starts with the formation of radical initiators from the TBHP mediated by the catalyst (**bcmim-Cu**). The initial rad-

ical interacts with the formamide generating the *N,N*-diethylcarbamoyl radical, which can evolve via to possible pathways. In path (a), decarbonylation of the carbamoyl radical forms the diethylaminyl radical, which reacts with the acid to form the product. In path (b), *N,N*-diethylcarbamoyl radical reacts with the acid to form *N,N*-diethyl carbamic 3-methylbenzoic anhydride, which releases CO₂ to produce the final amide.



Scheme 2. Possible reaction mechanism.

3. Materials and Methods

All commercially available reagents were purchased (Acros, Aldrich, Fluka) and used without further purification. Melting points were determined using a Gallenkamp capillary melting point apparatus (model MPD 350 BM 2.5) and are uncorrected. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded at the Research Technical Services of the University of Alicante (SSTTI-UA; <https://sstti.ua.es/en>, accessed on 1 June 2022), employing a Bruker AC-300. Chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hz. Deuterated chloroform (CDCl₃) was used as solvent and tetramethylsilane (TMS) was used as internal standard. Low-resolution mass spectra (LRMS) with electronic ionization (EI) were obtained with an Agilent GC/MS-5973 Network spectrometer provided with an EI source (70 eV) and helium as mobile phase. Samples were introduced by injection through a gas chromatograph Hewlett-Packard HP-6890, equipped with a Hp-5MS column (30 m length, 0.25 mm internal diameter and 0.25 μm film thickness: crosslinking 5% PH ME siloxane). Detected fragmentations are given as *m/z* with relative intensities in parenthesis (%). The conversion of the reactions and purity of the products were determined by gas chromatography (GC) analysis employing a Younglin 6100GC, equipped with a flame ionization detector and a Phenomenex ZB-5MS column (30 m length, 0.25 mm internal diameter and 0.25 μm film thickness: crosslinking 5% PH ME siloxane), using nitrogen (2 mL/min) as carrier gas and 270 °C in the injector block. The standard injection method was 60 °C as initial temperature (held for 3 min) and 15 °C/min until to 270 °C (held for 10 min). Infrared (IR) spectra were recorded with a FT-IR 4100 LE (JASCO, Pike Miracle ATR) spectrometer. Spectra were recorded from neat samples and wavenumbers (ν) are given in cm⁻¹.

Synthesis of 1,3-bis(carboxymethyl)imidazole (**bcmim**) [16]. A mixture of glycine (200 mmol, 15.0 g), glyoxal (40% aq., 100 mmol, 11.4 mL) and formaldehyde (36% aq., 100 mmol, 7.7 mL) was stirred at 95 °C for 2 h. After cooling down, the resultant brown precipitate was filtered and washed using cold water to obtain a white solid. The remaining water was co-evaporated with methanol under reduced pressure to afford **bcmim** as a white solid in 89% yield. The spectroscopic and analytical characterization of **bcmim** was previously reported by our research group [16].

Synthesis of MOF **bcmim-Cu** [11]. The ligand **bcmim** (26.1 mmol, 4.8 g) and copper(II) acetate (25.7 mmol, 4.7 g) were stirred in water (93 mL) after complete solution. Then, methanol (466 mL) was added to the aqueous solution, obtaining a light blue suspension. After leaving the mixture standing for 2 h, the solid was filtered and rinsed with methanol

to afford material **bcmim-Cu** as a blue powder in >99% yield. The spectroscopic and analytical characterization of material **bcmim-Cu** was previously reported by our research group [11].

Synthesis of *N,N*-diethyl-3-methylbenzamide (DEET). The 3-toluic acid (10 mmol, 1.4 g) and **bcmim-Cu** (10 mol%, 0.43 g) were placed in a round-bottom flask, followed by the addition of *N,N*-diethylformamide (180 mmol, 20 mL). The mixture was stirred at 100 °C while *tert*-butyl hydroperoxide (TBHP, 70% aq., 30 mmol, 4.15 mL) was added slowly over a period of 180 min employing an addition pump, keeping the flask open. The mixture was allowed to cool down to room temperature and the excess amount of starting amide was removed by distillation (10^{-4} mbar, 55–90 °C), and the residue was filtered through a pad of silica gel (2 g) eluting with a mixture 1:1 of hexane/ethyl acetate (20 mL). The solvent was removed under reduced pressure. Amide **1** was obtained as a pale-yellow oil in 95% yield. R_f (hexane/ethyl acetate, 1:1) = 0.58. IR (ATR): 2973, 2933, 2874, 1628 cm^{-1} . $^1\text{H-NMR}$ (300 MHz): 7.31–7.23 (m, 1H, H_{Ar}), 7.22–7.11 (m, 3H, $3 \times \text{H}_{\text{Ar}}$), 3.53, 3.26 (2 br s, 2H and 2H, $2 \times \text{CH}_2$), 2.37 (s, 3H, $\text{C}_{\text{Ar}}\text{CH}_3$), 1.34–0.98 (m, 6H, $2 \times \text{CH}_3$) ppm. $^{13}\text{C-NMR}$ (75 MHz): 171.5 (CO), 138.2, 137.3, ($\text{C}_{\text{Ar}}\text{Me}$, $\text{C}_{\text{Ar}}\text{CO}$), 129.8, 128.2, 126.9, 123.2 ($4 \times \text{C}_{\text{Ar}}$), 43.3, 39.2 ($2 \times \text{CH}_2$), 21.4 ($\text{C}_{\text{Ar}}\text{CH}_3$), 14.2, 13.0 ($2 \times \text{CH}_3$) ppm. LRMS (GC/MS-EI): m/z 191 [M^+] (21%), 190 (45), 119 (100), 91 (32), 65 (10). EA (for $\text{C}_{12}\text{H}_{17}\text{NO}$): calculated C (75.35%), H (8.96%), N (7.32%); found C (75.29%), H (8.94%), N (7.28%).

4. Conclusions

To conclude, the efficiency of the metal-organic framework **bcmim-Cu** as a heterogeneous catalyst to synthesize compounds of interest, such as *N,N*-diethyl-3-methylbenzamide, in gram quantities has been proved. The design of a catalyst and its application methodology should allow, as in the case of **bcmim-Cu**, to carry out the synthesis of compounds in a sustainable way. The procedure is very effective with significant values of yield and environmental factor. The main drawback is related to the amount of the formamide employed as a coupling partner, but the beneficial effect of the recovery of this material and of the catalyst itself mitigates this problem. The process has a very high value of materials recovery parameter (93% of MRP). In addition, the evaluation of the procedure using the EcoScale semi-quantitative tool, which takes into consideration ecological and economic factors, rates this DEET synthesis as excellent (with a value of 76 out of 100).

Supplementary Materials: The supporting information can be downloaded online: $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra, the product characterization, the GC analysis, IR spectrum, UV-Vis spectrum and “Green Metrics” calculations.

Author Contributions: Conceptualization, M.A.-S. and I.M.P.; methodology, M.A.-S. and I.M.P.; validation, M.A.-S. and I.M.P.; formal analysis, M.A.-S. and I.M.P.; investigation, M.A.-S.; resources, I.M.P.; writing—original draft preparation, M.A.-S. and I.M.P.; writing—review and editing, M.A.-S. and I.M.P.; supervision, I.M.P.; project administration, I.M.P.; funding acquisition, M.A.-S. and I.M.P. All authors have read and agreed to the published version of the manuscript.

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