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Short Note

1,3-Bis(3-carboxypropyl)-1*H*-imidazole

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Abstract: The use of γ-aminobutyric acid (GABA) as a starting material in a multicomponent reaction has resulted in the preparation of the zwitterionic 1,3-bis(3-carboxypropyl)imidazole (bcpim). The synthesis of this imidazole derivative in a one-pot procedure with stoichiometric amounts of the corresponding reagents (formaldehyde, glyoxal, and GABA in a 1:1:2 ratio) has resulted in a straightforward and effective methodology, meaning a significant improvement from a sustainable point of view.

Keywords: imidazole; γ-aminobutyric acid; zwitterion; multicomponent reaction

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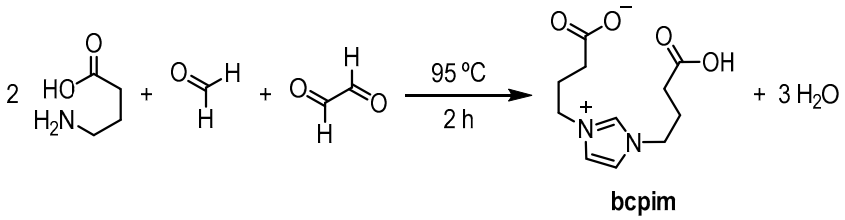
1. Introduction

Among the methods for the formation of imidazolium salts, the alkylation of the non-substituted nitrogen (N3) of a preformed 1-substituted imidazole ring by substitution with alkyl halides is one of the most employed. This methodology allows not only the introduction of aliphatic substituents [1], but also functionalized chains containing ethers [2], ketones [3,4], esters [5–8], and amides [9,10], among other functional groups. Alternatively, efficient and direct preparation of imidazolium salts was described by Arduengo in 1991 involving the direct formation of the 1,3-disubstituted imidazole motif via multicomponent reaction [11]. The reaction coupled two equivalents of an amine with an aldehyde and a 1,2-dicarbonyl compound in the presence of an acid acting as catalyst and source of the counterion. The reaction is similar to the Debus-Radziszewski-Japp reaction for the preparation of 2,4,5-trisubstituted imidazoles (using 2 equivalents of ammonia) and its variation presented by Drefahl and Herma in the preparation of 1,2,4,5-tetrasubstituted imidazoles (with 1 equivalent of ammonia and 1 equivalent of an organic amine) [12]. This synthetic strategy has been employed, more recently, with α-amino acids as nitrogen sources for the imidazole ring [13]. In these cases, no additional acid is needed since the amino acid provides the necessary acidic medium and the counterion in the final compound, which is obtained as a zwitterion. Our research group has optimized the preparation of the 1,3-bis(carboxymethyl)imidazole (**bcmim**) starting from glycine, glyoxal, and formaldehyde, and the transformation of **bcmim** in the corresponding halide salts [14]. This type of biscarboxy-imidazole derivatives has been useful as a precursor for the preparation of efficient and selective catalysts for sustainable organic transformations [14–19].

The preparation of analogues from other amino acid derivatives, such as γ-amino butanoic acid (GABA), has been only described by double substitution of a preformed imidazole ring. The addition of two equivalents of methyl 4-chlorobutanoate to 1-trimethylsilylimidazole gave the corresponding 1,3-bis [3-(methoxycarbonyl)propyl]imidazolium chloride, which was treated with hydrochloric acid to hydrolyze the ester moieties forming 1,3-bis(3-carboxypropyl)imidazolium chloride (**bcpim-Cl**). The treatment of **bcpim-Cl** with a mild base, such as triethylamine, was sufficient to afford the corresponding zwitterion 1,3-bis(3-carboxypropyl)imidazole (**bcpim**) [20,21]. Based on our experience, it is postulated that the synthesis of this compound (**bcpim**), using GABA in the multicomponent reaction to form the imidazole ring, will result in a more sustainable and environmentally benign synthetic process. Herein, we present our studies in this regard.

2. Results and Discussion

The formation of an imidazole ring from simple precursors by a multicomponent reaction represents a straightforward and suitable process. In addition, bond formation by simple condensation reactions leads to a process with high atomic economy (AE), where only water is generated as a by-product of the reaction. The reaction of formaldehyde, glyoxal, and GABA in a stoichiometric ratio of 1:1:2 results in the formation of 1,3-bis(3-carboxypropyl)imidazole (**bcpim**) and water in a ratio of 1:3 (Scheme 1). According to the procedure employed in the preparation of previous biscarboxy-imidazole derivatives [14], the reaction was carried out with stoichiometric amounts of the reagents at 95 °C, without the addition of any additional solvent. Thus, the reaction took place in the aqueous solution provided by the carbonyl compounds reagents (i.e., formaldehyde 37% *w*/*w* aq., and glyoxal 40% *w*/*w* aq.). After the reaction time (ca. 2 h), the product was precipitated from the reaction mixture employing methanol and diethyl ether. Notably, the expected product **bcpim** resulted to be soluble in the aqueous reaction solution, which is in contrast with its α-amino acid-derived counterparts [13,14].



Scheme 1. General scheme for the multicomponent reaction of formaldehyde, glyoxal, and GABA.

The ^{1}H and ^{13}C-NMR spectra were recorded in D_2O, both showing clear evidence of a C2 symmetry axis in the molecule (C2 to the C4-C5 bond), as expected (see Supplementary Materials). The MS analysis by electronic ionization (EI) was obtained from the pure product using direct insertion of the sample. The first significant peak presents a value of 154 *m*/*z*, which is possibly related to the fragment $[C_7H_{10}N_2O_2]^{+\bullet}$ being formed from the initial compound (M^+, *m*/*z* 240) by the elimination of a stable γ-butyrolactone molecule (see Supplementary Materials). The base peak (*m*/*z* 82), possibly related to ion $[C_4H_6N_2]^{+\bullet}$, can be formed by a McLafferty-type rearrangement from the fragment with *m*/*z* 154 by elimination of an acrylic acid molecule (see Supplementary Materials). The elimination of a water molecule from the fragment $[C_7H_{10}N_2O_2]^{+\bullet}$ (*m*/*z* 154) provides the ion $[C_7H_8N_2O]^{+\bullet}$ with *m*/*z* 136 (see Supplementary Materials). A rearrangement of the fragment $[C_7H_{10}N_2O_2]^{+\bullet}$ (*m*/*z* 154) generates an acetyloxy radical and a $[C_5H_7N_2]^{+}$ cation (*m*/*z* 95), which can form the 1,4-diazaepinium cation (see Supplementary Materials).

At this point, the evaluation of the environmental impact of the synthetic procedure was considered by measuring the environmental factor. The E-factor is 8.41 (mass of waste per unit mass of product), for which the solvents employed for the final purification are the main factor contributing to the generated waste of this procedure (Table 1 and Supplementary Materials). To compare with the previously reported protocol, the sum of the materials employed in the three reaction steps described in reference [20] has been considered. As presented in Table 1, the protocol starting from 1-trimethylsilylimidazole formed the expected product **bcpim** with an E-factor of 93.34 (more than 10 times larger than the multicomponent methodology reported herein). Moreover, considering the analytic tool EcoScale [22] to evaluate the organic synthesis of **bcpim**, the preparation of **bcpim** from GABA resulted in a score of 80 (out of 100) which is considered an excellent synthetic procedure (Table 1 and Supplementary Materials). In contrast, the previously reported methodology starting from 1-trimethylsilylimidazole scored 58 in the EcoScale, which would be considered an acceptable protocol (EcoScale score > 50), but still significantly worse than our synthetic methodology (Table 1 and Supplementary Materials).

Table 1. E-factor profile and EcoScale scores for the synthesis of 1,3-bis(3-carboxypropyl)imidazole (**bcpim**) [1].

Parameter		Value	
		This Work	**Ref. [20]**
E-factor (Total)		8.41	93.34
	E-factor (kernel)	0.43	1.71
	E-factor (excess)	0.00	0.09
	E-factor (catalyst)	0.00	0.00
	E-factor (solvent)	0.67	13.33
	E-factor (work-up)	0.00	0.00
	E-factor (purification)	7.31	78.21
EcoScale		80	58

[1] For details of calculation, see Supplementary Materials.

To further evaluate the impact of our methodology, different metrics, such as atom economy (AE), stoichiometric factor (SF), reaction mass efficiency (RME), materials recovery parameter (MRP), and reaction yield (RY) have been determined (Table 2) [23]. In general terms, the parameters for our novel protocol are better than those of the previously reported procedure (Table 2), as is shown in the radial-pentagon diagram (Figure 1). While the overall yield (87 vs. 90%) and the stoichiometric factor are comparable in both methodologies, the atom economy of the multicomponent reaction is twice the one from the multistep protocol (82 vs. 41%). Reaction mass efficiency is 10 times higher, and the materials recovery parameter is five times higher, in the new protocol (Table 2). Moreover, the combination of the overall material efficiency parameters of RY, AE, 1/SF, MRP, and RME in a vector magnitude ratio (VMR) can provide unbiased quantification of the overall degree of greenness. The VMR was calculated according to Equation 1 [23], giving a value of 0.702 for the preparation of **bcpim** using the protocol described in this work. In contrast, the multistep protocol has a lower value of VMR (0.619, Table 2).

$$\mathrm{VMR} = \frac{1}{\sqrt{5}}\left[\sqrt{(\mathrm{RY})^2 + (\mathrm{AE})^2 + \left(\frac{1}{\mathrm{SF}}\right)^2 + (\mathrm{MRP})^2 + (\mathrm{RME})^2}\right] \quad (1)$$

Table 2. Green metrics for the synthesis of 1,3-bis(3-carboxypropyl)imidazole (**bcpim**).

Parameter	Value (%) [1]	
	This Work	**Ref. [20]**
Reaction yield (RY)	(87%)	(90%)
Atom economy (AE)	0.816 (82%)	0.409 (41%)
Stoichiometric factor (SF)	0.999	1.032
1/SF	1.00 (100%)	0.969 (97%)
Reaction mass efficiency (RME)	0.108 (11%)	0.011 (1%)
Materials recovery parameter (MRP)	0.152 (15%)	0.030 (3%)
Vector magnitude ratio (VMR) [2]	0.702	0.619

[1] Some parameters can be expressed as a percentage (in brackets). [2] Determined according to Equation (1).

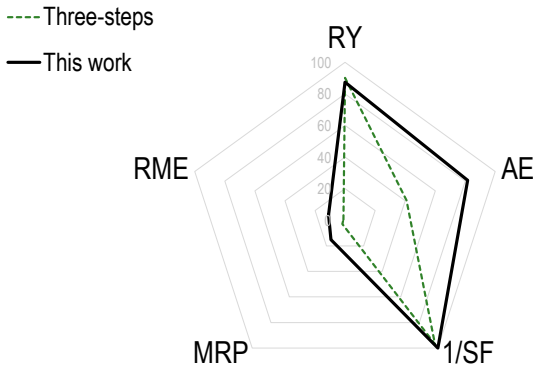


Figure 1. Radial-pentagon diagram with metrics (%): reaction yield (RY), atom economy (AE), reaction mass efficiency (RME), mass recovery parameter (MRP), and inverse of stoichiometric factor (1/SF). Comparison of both methodologies: multistep reaction [20], and one-step reaction in this work.

3. Materials and Methods

All commercially available reagents were purchased (Acros, Aldrich, and 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. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at the Research Technical Services of the University of Alicante, Alicante, Spain (SSTTI-UA; https://sstti.ua.es/en; accessed on 2 November 2022), employing a Bruker AC-300 (Madrid, Spain). Chemical shifts (δ) are given in ppm, and the coupling constants (*J*) are given in Hz. Deuterated water (D_2O) was used as solvent, and residual water (HOD) was used as internal standard. Low-resolution mass spectrum (LRMS) with electronic ionization (EI) was obtained at the Research Technical Services of the University of Alicante (SSTTI-UA; https://sstti.ua.es/en) with an Agilent model 5973 Network mass spectrometer(Madrid, Spain) with a direct introduction of the sample to the ionic source using the SIS Direct Insertion Probe (73DIP-1). The mass spectrometer is equipped with a single electronic impact source as well as a quadrupole analyzer. Detected fragmentations are given as *m/z* with relative intensities in parenthesis (%). Infrared (IR) spectrum was recorded with a FT-IR 4100 LE (JASCO, Pike Miracle ATR, PIKE Technologies, Fitchburg, WI, USA) spectrometer from neat sample and wavenumbers (ν) are given in cm^{-1}.

The synthesis of 1,3-bis(3-carboxymethyl)imidazole (**bcpim**) is considered. A mixture of γ-aminobutanoic acid (GABA, 20 mmol, 2.06 g), glyoxal (40% aq., 10 mmol, 1.14 mL) and formaldehyde (37% aq., 10 mmol, 0.75 mL) was stirred at 95 °C for 2 h. After cooling down, methanol (10 mL) and diethyl ether (10 mL) were subsequently added to the stirring mixture. The resultant brownish precipitate was filtered and washed using cold diethyl ether (10 mL) to obtain a tan solid (2.1 g, 87% yield). IR (ATR): ν 3132, 3105, 2981 (COO-H, st), 2862 (C-H, st), 1709, 1666 (C=O, st), 1562 [$(COO)^{-}$, st as], 1404 [$(COO)^{-}$, st si] cm^{-1}; ^{1}H-NMR (300 MHz, D_2O): δ_H 8.85 (s, 1H, NCHN-imidazole ring, 7.54 (d, J = 1.6 Hz, 2H, NCHCH-imidazole ring), 4.26 (t, J = 7.1 Hz, 4H, 2 × NCH_2), 2.35 (t, J = 7.2 Hz, 4H, 2 × CH_2CO_2), 2.17 (m, 4H, 2 × CH_2) ppm; ^{13}C-NMR (75 MHz, D_2O): δ_C 179.0 (CO_2), 135.5 (NCN-imidazole ring), 122.5 (NCCN-imidazole ring), 48.9 (NCH_2), 32.0 ($\underline{C}H_2CO_2$), 25.4 ($NCH_2\underline{C}H_2$) ppm; LRMS (DIP-EI): *m/z* 240 (M^{+}, 0.3%), 156 (21), 155 (56), 154 (68), 138 (13), 137 (42), 135 (64), 110 (12), 109 (22), 108 (22), 107 (16), 96 (21), 95 (50), 94 (13), 87 (13), 86 (23), 83 (39), 82 (100), 81 (83), 80 (28), 69 (19), 68 (28), 67 (12), 56 (19), 55 (28), 54 (31), 53 (18), 52 (11), 45 (16), 43 (20), 42 (54), 41 (44), 40 (17).

4. Conclusions

To summarize, a simple and efficient multicomponent reaction has been developed for the preparation of 1,3-bis(3-carboxypropyl)imidazole (**bcpim**), being able to carry out the reaction in gram scale. In addition, based on different metrics (RY, AE, SF, MRP, RME,

EcoScale, E-factor, and VMR), it has been proved that the multicomponent protocol is better, in terms of sustainability and environmental impact, than the previously reported methodology for the preparation of this compound. Among these parameters, the EcoScale and the VMR have been used for the unbiased comparison of the overall greenness, evidencing significantly improved results.

Supplementary Materials: The following are available online: copies of ^{1}H-NMR, ^{13}C-NMR, IR, MS spectra of compound **bcpim.**

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Data Availability Statement: The data presented in this study are available in Supplementary Materials.

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