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One-pot synthesis of β-imidazolylpropionamides

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Abstract

New efficient one-pot methodology for the preparative synthesis of β-imidazolylpropionamides was elaborated. It is based on the addition of imidazole to the activated double bond of the intermediate acrylimidazolide in the reaction between diverse acrylic acids and different amines promoted by CDI. A set of structurally and functionally diverse β-imidazolylpropionamides was obtained in high preparative yields.

Keywords: β-Imidazolylpropionamides; Carbonyldiimidazole (CDI); Acylation; Acrylic acids

1. Introduction

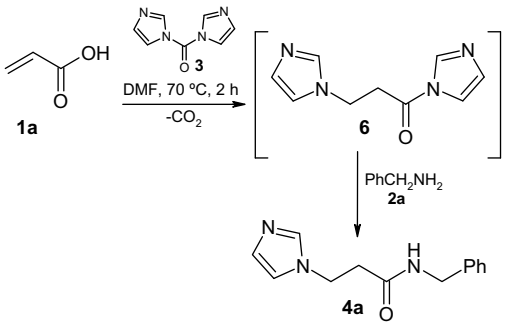
β-Imidazolylpropionamides are mimetics of histidine, possess anticonvulsant activities, and are considered as promising antiepileptic agents with excellent pharmacocinetics.[1] These compounds can be prepared through the acylation of amines by β-imidazolylpropionyl chlorides,[2] through the addition of imidazole to acrylamides,[3] or via the alkylation of imidazole by β-chloropropionamides.[1b,c] Rather narrow scope, complicated with purification procedures and moderate or low yields limit the use of these procedures in combinatorial synthesis of diverse drug-like β-imidazolylpropionamides.

Herein, we report a facile and versatile method for the synthesis of β-imidazolylpropionamides, which is based on the one-pot reaction of acrylic acids **1** with amines **2** in the presence of carbonyldiimidazole **3** (CDI) as a condensing agent and donor of imidazole.

2. Results and discussion

Serendipitously, we found that the reaction of acrylic acid **1a** with benzylamine **2a** in the presence of CDI as a condensing agent[4] resulted benzylamide of β-imidazolylpropionamide **4a** (Scheme 1).

The model experiments revealed that under the reaction conditions imidazole did not add to the double bond of benzylacrylamide **5a**[5] (Scheme 2).



Scheme 1.

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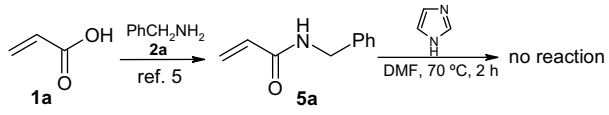
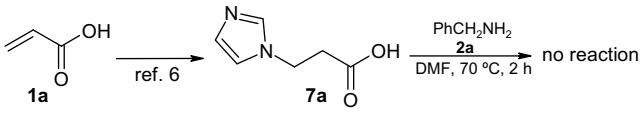
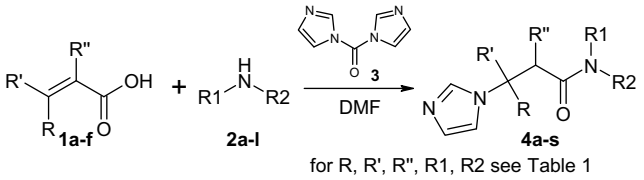


Scheme 2.



Scheme 3.

This indicates that the addition of imidazole to the acrylic double bond occurs prior to the formation of the amide bond. It seems plausible that compound **4a** is formed through the reaction of activated intermediate **6** with benzylamine. Compound **6** is likely to be formed through the amidation of acrylic acid with CDI followed by the addition of imidazole to the acrylic double bond activated through electronwithdrawing effect of the amide fragment.



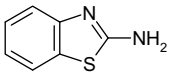
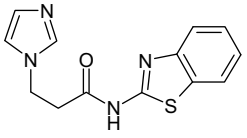
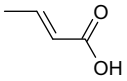
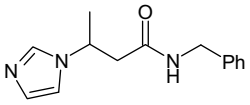
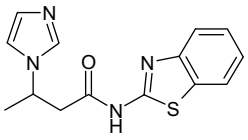
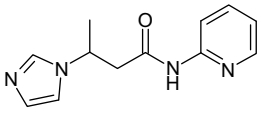
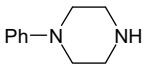
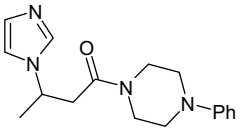
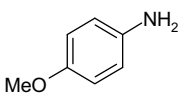
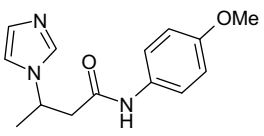
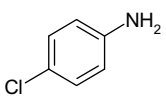
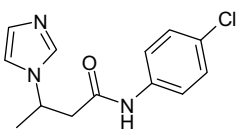
Scheme 4.

The formation of compound **6** was detected by ^{1}H NMR spectroscopy of a solution containing acid **1a** and CDI: two triplets of the methylene protons of **6** appeared instead of the vinyl protons of acrylic acid. This conclusion is further supported by the following model studies. β-Imi-

Table 1
Structures,[a] yields,[b] melting points,[c] typical NMR data,[d] and M+1[e] for products type **4**[g]

Entry	Acid	Amine	Product	Yield (%)	Mp (°C)	Typical NMR data	M+1
1	**1a**	**2a**	**4a**	94	Oil	$\delta = 2.64$ (t, $^{3}J_{HH} = 6.3$ Hz, 2H, COCH_2CH$_2$), 4.22 (t, $^{3}J_{HH} = 6.3$ Hz, 2H, COCH$_2$$CH_2$), 4.27 (d, $^{3}J_{HH} = 5.4$ Hz, 2H, CH_2NH), 6.88 (s, 1H, CH$_{im.}$), 7.11 (s, 1H, CH$_{im.}$), 7.16 (d, $^{3}J_{HH} = 7.2$ Hz, 2H, 2CH$_{Ph}$), 7.23 (t, $^{3}J_{HH} = 7.1$ Hz, 1H, CH$_{Ph}$), 7.25 (t, $^{3}J_{HH} = 7.9$ Hz, 2H, 2CH$_{Ph}$), 7.58 (s, 1H, CH$_{im.}$), 8.48 (br t, 1H)	230
2	**1a**	**2b**	**4b**	89	Oil	$\delta = 2.80$ (t, $^{3}J_{HH} = 6.9$ Hz, 2H, COCH_2CH$_2$), 3.36 (m, 2H, CH$_{2morph.}$), 3.42 (m, 2H, CH$_{2morph.}$), 3.49 (m, 4H, CH$_{2morph.}$), 4.14 (t, $^{3}J_{HH} = 6.9$ Hz, 2H, COCH$_2$$CH_2$), 6.84 (s, 1H, CH$_{im.}$), 7.15 (s, 1H, CH$_{im.}$), 7.60 (s, 1H, CH$_{im.}$)	210
3	**1a**	**2c**	**4c**	91	117	$\delta = 2.89$ (br t, 2H, COCH_2CH$_2$), 4.27 (t, $^{3}J_{HH} = 6.2$ Hz, 2H, COCH$_2$$CH_2$), 6.87 (s, 1H, CH$_{im.}$), 7.18 (m, 2H, CH$_{im.}$, CH$_{Ph}$), 7.18 (t, $^{3}J_{HH} = 7.2$ Hz, 1H, CH$_{Ph}$), 7.46 (d, $^{3}J_{HH} = 7.2$ Hz, 1H, CH$_{Ph}$), 7.63 (m, 2H, CH$_{im.}$, CH$_{Ph}$), 9.62 (s, 1H, NH)	250
4	**1a**	**2d**	**4d**	78	90	$\delta = 1.06$ (d, $^{3}J_{HH} =$ Hz, 6H, CH(CH_3)$_2$), 2.80 (t, $^{3}J_{HH} = 6.1$ Hz, 2H, COCH_2CH$_2$), 2.95 (m, 1H, CH(CH$_3$)$_2$), 4.26 (t, $^{3}J_{HH} = 6.1$ Hz, 2H, COCH$_2$$CH_2$), 6.88 (s, 1H, CH$_{im.}$), 7.14 (m, 4H, CH$_{im.}$, 3CH$_{Ph}$), 7.28 (d, $^{3}J_{HH} = 7.6$ Hz, 1H, CH$_{Ph}$), 7.59 (s, 1H, CH$_{im.}$), 9.41 (s, 1H, NH)	258
5	**1a**	**2e**	**4e**	95	142	$\delta = 1.01$ (br t, 6H, CH_3CH$_2$), 2.83 (br t, 2H, COCH_2CH$_2$), 3.13 (br q, 4H, 2CH$_3$$CH_2$), 4.27 (br t, 2H, COCH$_2$$CH_2$), 8.85 (s, 1H, CH$_{im.}$), 7.14 (s, 1H, CH$_{im.}$), 7.42 (d, $^{3}J_{HH} = 7.0$ Hz, 1H, CH$_{Ph}$), 7.50 (t, $^{3}J_{HH} = 7.0$ Hz, 1H, CH$_{Ph}$), 7.60 (s, 1H, CH$_{Ph}$), 7.73 (d, $^{3}J_{HH} = 7.0$ Hz, 1H, CH$_{Ph}$), 8.09 (s, 1H, CH$_{im.}$), 10.32 (s, 1H, NH)	351

Table 1 (*continued*)

Entry	Acid	Amine	Product	Yield (%)	Mp (°C)	Typical NMR data	M+1
6	**1a**	 **2f**	 **4f**	98	208	$\delta = 3.01$ (t, $^3J_{HH} = 6.5$ Hz, 2H, $CO\mathit{CH}_2CH_2$), 4.32 (t, $^3J_{HH} = 6.5$ Hz, 2H, $COCH_2\mathit{CH}_2$), 6.86 (s, 1H, $CH_{im.}$), 7.14 (s, 1H, $CH_{im.}$), 7.27 (t, $^3J_{HH} = 7.3$ Hz, 1H, $CH_{benzotiazol}$), 7.41 (t, $^3J_{HH} = 7.3$ Hz, 1H, CH_{btz}), 7.62 (s, 1H, $CH_{im.}$), 7.71 (d, $^3J_{HH} = 7.3$ Hz, 1H, CH_{btz}), 7.94 (d, $^3J_{HH} =$ Hz, 1H, CH_{btz}), 12.6 (br s, 1H, NH)	273
7	 **1b**	**2a**	 **4g**	94	Oil	$\delta = 1.41$ (d, $^3J_{HH} = 6.7$ Hz, 3H, CH_3CH), 2.61 (m, 2H, CH_2CH), 4.17 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2NH), 4.25 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2NH), 4.69 (m, 1H, $CH_2\mathit{CH}$), 6.88 (s, 1H, $CH_{im.}$), 7.07 (d, $^3J_{HH} =$ Hz, 2H, $2CH_{Ph}$), 7.08 (m, 2H, $CH_{im.}$, CH_{Ph}), 7.24 (m, 2H, $2CH_{Ph}$), 7.63 (s, 1H, $CH_{im.}$), 7.41 (br t, 1H)	244
8	**1b**	**2f**	 **4h**	97	193	$\delta = 1.48$ (d, $^3J_{HH} =$ Hz, 3H, CH_3CH), 3.04 (m, 2H, CH_2CH), 4.82 (m, 1H, $CH_3\mathit{CH}$), 6.87 (s, 1H, $CH_{im.}$), 7.24 (s, 1H, $CH_{im.}$), 7.27 (t, $^3J_{HH} = 7.7$ Hz, 1H, CH_{btz}), 7.40 (t, $^3J_{HH} = 7.7$ Hz, 1H, CH_{btz}), 7.7 (m, 2H, $CH_{btz,}$ $CH_{im.}$), 7.93 (d, $^3J_{HH} = 7.7$ Hz, 1H, CH_{btz}), 12.44 (s, 1H, NH)	287
9	**1b**	**2g**	 **4i**	79	Oil	$\delta = 1.44$ (d, $^3J_{HH} = 6.7$ Hz, 3H, CH_3CH), 2.84 (dd, $^3J_{HH} = 8.1$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2CH), 2.97 (dd, $^3J_{HH} = 8.1$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2CH), 4.77 (m, 1H, $CH_3\mathit{CH}$), 6.87 (s, 1H, $CH_{im.}$), 7.05 (t, $^3J_{HH} = 8.0$ Hz, 1H, CH_{Py}), 7.21 (s, 1H, $CH_{im.}$), 7.71 (s, 1H, $CH_{im.}$), 7.73 (t, $^3J_{HH} = 8.0$ Hz, 1H, CH_{Py}), 8.01 (d, $^3J_{HH} = 8.0$ Hz, 1H, CH_{Py}), 8.27 (d, $^3J_{HH} = 4.0$ Hz, 1H, CH_{Py}), 10.54 (s, 1H, NH)	231
10	**1b**	 **2h**	 **4j**	90	Oil	$\delta = 1.42$ (d, $^3J_{HH} = 6.5$ Hz, 3H, CH_3CH), 2.81 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 15.9$ Hz, 1H, CH_2CH), 2.87 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 15.9$ Hz, 1H, CH_2CH), 2.96 (m, 2H, $CH_{2\,pipi}$), 3.08 (m, 2H, $CH_{2\,pipi}$), 3.53 (m, 4H, $CH_{2\,pipi}$), 4.68 (m, 1H, $CH_3\mathit{CH}$), 6.79 (t, $^3J_{HH} = 7.1$ Hz, 1H, CH_{Ph}), 6.83 (s, 1H, $CH_{im.}$), 6.92 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.21 (m, 3H, $2CH_{Ph}$, $CH_{im.}$), 7.65 (s, 1H, $CH_{im.}$)	299
11	**1b**	 **2i**	 **4k**	80	Oil	$\delta = 1.44$ (d, $^3J_{HH} = 6.7$ Hz, 3H, CH_3CH), 2.77 (m, 2H, CH_2CH), 3.68 (s, 3H, OCH_3), 4.76 (m, 1H, $CH_3\mathit{CH}$), 6.84 (d, $^3J_{HH} = 8.9$ Hz, 2H, $2CH_{Ph}$), 6.88 (s, 1H, $CH_{im.}$), 7.22 (s, 1H, $CH_{im.}$), 7.43 (d, $^3J_{HH} = 8.9$ Hz, 2H, $2CH_{Ph}$), 7.69 (s, 1H, $CH_{im.}$), 9.88 (s, 1H, NH)	260
12	**1b**	 **2j**	 **4l**	88	123	$\delta = 1.44$ (d, $^3J_{HH} = 6.6$ Hz, 3H, CH_3CH), 2.79 (d, $^3J_{HH} = 7.0$ Hz, 2H, CH_2CH), 4.74 (m, 1H, $CH_3\mathit{CH}$), 6.85 (s, 1H, $CH_{im.}$), 7.21 (s, 1H, $CH_{im.}$), 7.31 (d, $^3J_{HH} = 8.3$ Hz, 2H, $2CH_{Ph}$), 7.53 (d, $^3J_{HH} = 8.3$ Hz, 2H, $2CH_{Ph}$), 7.65 (s, 1H, $CH_{im.}$), 10.08 (s, 1H, NH)	264

(*continued on next page*)

Table 1 (*continued*)

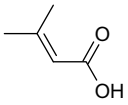
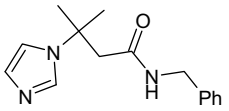
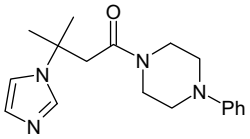
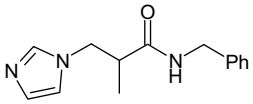
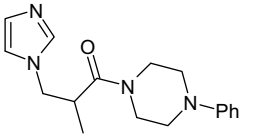
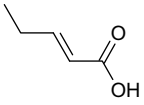
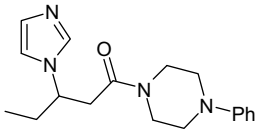
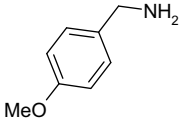
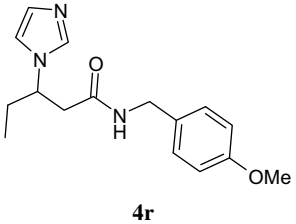
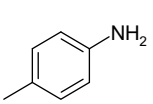
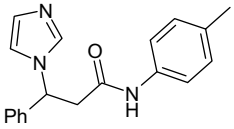
Entry	Acid	Amine	Product	Yield (%)	Mp (°C)	Typical NMR data	M+1
13	 **1c**	**2a**	 **4m**	65	Oil	$\delta = 1.60$ (s, 6H, $2CH_3$), 2.67 (s, 2H, $CH_2(CH_3)_2$), 4.21 (d, $^3J_{HH} = 5.7$ Hz, 2H, CH_2NH), 6.89 (s, 1H, $CH_{im.}$), 7.13 (d, $^3J_{HH} = 7.3$ Hz, 2H, $2CH_{Ph}$), 7.14 (m, 4H, $CH_{im.}$, $3CH_{Ph}$), 7.71 (s, 1H, $CH_{im.}$), 8.36 (br t, 1H, NH)	258
14	**1c**	**2h**	 **4n**	73	149	$\delta = 1.64$ (s, 6H, $CH_2(CH_3)_2$), 2.88 (s, 2H, $CH_2(CH_3)_2$), 2.98 (m, 4H, $2CH_{2\,pipi}$), 3.40 (m, 2H, $CH_{2\,pipi}$), 3.51 (m, 2H, $CH_{2\,pipi}$), 6.78 (t, $^3J_{HH} = 7.1$ Hz, 1H, CH_{Ph}), 6.85 (s, 1H, $CH_{im.}$), 6.90 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.20 (t, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.29 (s, 1H, $CH_{im.}$), 7.71 (s, 1H, $CH_{im.}$)	313
15	 **1d**	**2a**	 **4o**	95	90	$\delta = 1.02$ (d, $^3J_{HH} = 6.7$ Hz, 3H, CH_3CH), 2.79 (m, 1H, CH_3CH), 3.93 (dd, $^3J_{HH} = 5.7$ Hz, $^2J_{HH} = 13.4$ Hz, 1H, CH_2CH), 4.14 (dd, $^3J_{HH} = 5.7$ Hz, $^2J_{HH} = 13.4$ Hz, 1H, CH_2CH), 4.19 (dd, $^3J_{HH} = 6.0$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2NH), 4.27 (dd, $^3J_{HH} = 6.0$ Hz, $^2J_{HH} = 15.1$ Hz, 1H, CH_2NH), 6.86 (s, 1H, $CH_{im.}$), 7.04 (s, 1H, $CH_{im.}$), 7.08 (d, $^3J_{HH} = 7.4$ Hz, 2H, $2CH_{Ph}$), 7.20 (t, $^3J_{HH} = 7.1$ Hz, 1H, CH_{Ph}), 7.27 (t, $^3J_{HH} = 7.4$ Hz, 2H, $2CH_{Ph}$), 7.52 (s, 1H, $CH_{im.}$), 8.40 (br t, 1H)	244
16	**1d**	**2h**	 **4p**	90	85	$\delta = 0.99$ (d, $^3J_{HH} = 6.3$ Hz, 3H, CH_3CH), 2.91 (m, 2H, $CH_{2\,pipi}$), 3.07 (m, 2H, $CH_{2\,pipi}$), 3.35 (m, 1H, CH_3CH), 3.53 (m, 3H, 3 CH_{pipi}), 3.62 (m, 1H, CH_{pipi}), 3.97 (dd, $^3J_{HH} = 8.4$ Hz, $^2J_{HH} = 13.3$ Hz, 1H, CH_2CH), 4.14 (dd, $^3J_{HH} = 8.4$ Hz, $^2J_{HH} = 13.3$ Hz, 1H, CH_2CH), 6.79 (t, $^3J_{HH} = 7.1$ Hz, 1H, CH_{Ph}), 6.80 (s, 1H, CH_{im}), 6.89 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.13 (s, 1H, CH_{im}), 7.20 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.56 (s, 1H, CH_{im})	299
17	 **1e**	**2h**	 **4q**	88	Oil	$\delta = 0.66$ (t, $^3J_{HH} = 7.2$ Hz, 3H, CH_3CH_2), 1.75 (m, 2H, CH_3CH_2), 2.82 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 15.9$ Hz, 1H, CH_2CH), 2.95 (m, 3H, CH_2CH, $CH_{2\,pipi}$), 3.09 (m, 2H, $CH_{2\,pipi}$), 3.54 (m, 4H, $2CH_{2\,pipi}$), 4.44 (m, 1H, CH_2CH), 6.78 (t, $^3J_{HH} = 7.1$ Hz, 1H), 6.85 (s, 1H, $CH_{im.}$), 6.91 (d, $^3J_{HH} = 7.9$ Hz, 2H, $2CH_{Ph}$), 7.20 (m, 3H, $2CH_{Ph}$, $CH_{im.}$), 7.63 (s, 1H, $CH_{im.}$)	313
18	**1e**	 **2k**	 **4r**	86	Oil	$\delta = 0.62$ (t, $^3J_{HH} = 7.1$ Hz, 3H, CH_3CH_2), 1.71 (m, 2H, CH_3CH_2), 2.62 (d, $^3J_{HH} = 7.1$ Hz, 2H, CH_2NH), 3.55 (s, 3H, OCH_3), 4.06 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 14.8$ Hz, 1H, CH_2CH), 4.16 (dd, $^3J_{HH} = 5.5$ Hz, $^2J_{HH} = 14.8$ Hz, 1H, CH_2CH), 4.45 (m, 1H, CH_2CH), 6.80 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 6.88 (s, 1H, $CH_{im.}$), 6.95 (d, $^3J_{HH} = 8.2$ Hz, 2H, $2CH_{Ph}$), 7.13 (s, 1H, $CH_{im.}$), 7.58 (s, 1H, $CH_{im.}$), 8.28 (br r, 1H, NH)	288

Table 1 (*continued*)

Entry	Acid	Amine	Product	Yield (%)	Mp (°C)	Typical NMR data	M+1
19	**1f**	 **2l**	 **4s**	56	195	$\delta = 2.21$ (s, 3H, CH_3Ph), 3.25 (dd, $^3J_{HH} = 6.2$ Hz, $^2J_{HH} = 15.2$ Hz, 1H, CH_2CH), 3.35 (dd, $^3J_{HH} = 9.3$ Hz, $^2J_{HH} = 15.2$ Hz, 1H, CH_2CH), 5.89 (m, 1H, CH_2CH), 6.88 (s, 1H, $CH_{im.}$), 7.06 (d, $^3J_{HH} = 7.9$ Hz, 2H, $2CH_{Ph}$), 7.29 (m, 2H, $CH_{im.}$, CH_{Ph}), 7.37 (m, 6H, (2+4)H_{Ph}), 7.81 (s, 1H, $CH_{im.}$), 9.95 (s, 1H, NH)	336

[a] Satisfactory microanalysis obtained C ± 0.33; H ± 0.45; N ± 0.25.
[b] Yields refer to pure isolated product. According to HPLC MS data all the synthesized compounds have purity >95%.
[c] Melting points were measured with a Buchi melting points apparatus and are uncorrected.
[d] ^{1}H NMR (500 MHz) were recorded on a Varian Mercury-400 and Bruker Avance DRX 500 spectrometers with TMS as an internal standard in DMSO-d_6.
[e] LC/MS spectra were recorded using chromatography/mass spectrometric system that consists of high-performance liquid chromatograph 'Agilent 1100 Series' equipped with diode-matrix and mass-selective detector 'Agilent LC/MSD SL'.

dazolylpropionic acid **7a**[6] did not react with benzylamine **2a** in the presence of CDI (under the acylation conditions of **1a**). This can be explained by low activity of the zwitterionic structure of acid **7a** (Scheme 3).

On the basis of the results described above we have found the conditions for the one-pot synthesis of structurally and functionally diverse compounds **4**. Equimolar amount of CDI was added to the DMF solution of acids **1a–e** and the reaction mixture was being heated at 70 °C for 2 h to ensure the formation of intermediate **6**. The latter was reacted with equimolar amount of amines **2a–e** at 100 °C (6 h) to give target compounds **4a–r** in 84–99% yields. Compounds **4a–r** could be easily isolated in pure form by precipitation or extraction.[7]

In the case of cinnamic acid **1f**, the yields of compounds **4** were considerably lower (55–60%)[8] most probably due to the lower activity of the allylic double bond conjugated with the phenyl ring (Scheme 4, Table 1).

The composition and structure of all the compounds were established through LC/MS, elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR of compounds contained one set of signals for the imidazole protons and two characteristic signals for α- and β-protons of the propionyl fragment.

3. Conclusion

Acrylic acids react with CDI to give active intermediate that can be readily transformed into various β-imidazolylpropionamides through the amidation with primary and secondary amines. The elaborated one-pot methodology is applicable to a variety of substituted acrylic acids and amines and affords structurally and functionally diverse target compounds in high preparative yields.

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References and notes

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5. Benzylacrylamide **5a** was obtained by the reaction of acrylic acid **1a** with benzylamine **2a** with *N*-methyl-2-chloropyridin iodide (Mukaiyama's reagent): Mukaiyama, T. *Angew. Chem.* **1979**, *91*, 798–812.
6. β-Imidazolylpropionic acid **7a** was obtained by the addition of imidazole to acrylic acid: Mroczkiewicz, A. *Acta Pol. Pharm.* **1984**, *41*, 435–440.
7. *General procedure.* Acid **1a–f** (2.2 mmol) and CDI (2.4 mmol) were placed in 15 mL tube and dissolved in 3–4 mL of DMF. The tube was heated at 70 °C for 2 h (caution: the tube must be opened for free evaporation of CO_2). After that, amine **2a–l** (2 mmol) was added, the tube was thoroughly sealed, and heated at 100 °C for 6 h. Then, the reaction mixture was diluted by 8–10 mL of water and sonicated at rt for 1–2 h (BRANSON 2510E-MT). The precipitate was filtered and washed with *i*-PrOH (2 mL). Targeted β-imidazolylpropionamides **4e**, **4f**, **4h**, **4n** were obtained as white powders. In the case of water-soluble compounds the extraction by DCM was used. DCM's solution washed with 2% aq solution of $NaHCO_3$ (8 mL). Targeted products **4a–d**, **4g**, **4i–m**, **4o–r** were formed after the evaporation of DCM.
8. β-Imidazolylpropionamide **4s** was synthesized by general procedure and isolated by preparative chromatography.
9. ^{13}C NMR analysis for targeted compounds: **4a**: $\delta = 37.3$, 42.6, 42.9, 119.8, 127.2, 127.7, 128.7, 128.7, 137.7, 139.7, 169.9; **4b**: $\delta = 34.2$, 41.9, 42.6, 45.6, 66.4, 119.9, 128.6, 137.9, 168.9; **4c**: 37.7, 42.7, 119.8, 126.8, 126.9, 127.2, 127.9, 128.8, 129.9, 135.1, 137.8, 169.5; **4d**: $\delta = 23.7$, 27.5, 37.6, 42.9, 119.7, 126.0, 126.1, 126.8, 127.4, 128.8, 134.9, 137.8, 143.9, 169.5; **4e**: $\delta = 14.5$, 38.3, 42.3, 42.4, 117.3, 119.7, 121.7, 123.1, 128.9, 130.4, 137.8, 140.1, 140.7, 169.6; **4f**: $\delta = 37.4$, 42.1, 119.8, 121.04, 122.2, 124.06, 126.6, 128.9, 131.9, 137.8, 148.9, 158.1, 170.3; **4g**: $\delta = 22.1$, 42.5, 43.7, 50.5, 117.7, 127.2, 127.5, 128.6, 128.7, 136.4, 139.7, 169.5; **4h**: $\delta = 21.9$, 43.5, 49.8, 117.7, 121.0, 122.1, 124.1, 126.6, 128.8, 131.9, 136.5, 148.9, 158.0, 169.7; **4i**: $\delta = 22.0$, 44.3, 50.2, 114.0, 117.7, 119.9, 128.7, 136.5, 138.6, 148.4, 152.2, 169.5; **4j**: $\delta = 22.3$, 41.4, 45,1, 48.7, 49.1, 50.3, 55.3, 116.3, 117.9, 119.8, 128.6, 129.4, 136.6, 151.2, 168.4; **4k**: $\delta = 21.9$, 44.5, 50.4, 55.6, 144.3, 117.8, 121.3, 128.6, 132.5, 136.5, 155.8, 168.0; **4l**: $\delta = 21.9$, 44.6, 50.2, 117.7, 121.2, 127.4, 128.8, 129.1, 136.5, 138.3, 168.7; **4m**: $\delta = 28.7$, 42.6, 48.4, 56.5, 117.6, 127.2, 127.7, 128.5, 128.7, 135.2, 139.7, 169.0; **4n**: $\delta = 28.8$, 41.2, 43.9, 45.6, 48.7,

49.0, 56.7, 116.3, 117.7, 119.8, 128.4, 129.5, 135.5, 151.2, 167.8; **4o**: $\delta = 16.0$, 42.0, 42.5, 49.4, 120.0, 127.2, 127.5, 128.6, 128.7, 137.9, 139.7, 173.6; **4p**: $\delta = 15.7$, 36.9, 41.5, 45.1, 48.7, 49.2, 49.7, 116.3, 119.8, 120.2, 128.6, 129.5, 138.1, 151.2, 172.3; **4q**: $\delta = 10.8$, 28.7, 38.9, 41.4, 45.2, 48.8, 49.1, 56.4, 116.3, 117.9, 119.8, 128.8, 129.4, 137.4, 151.2, 168.4; **4r**: $\delta = 10.7$, 28.7, 41.9, 42.0, 55.56, 56.52, 114.1, 117.9, 128.8, 131.6, 133.1, 137.2, 158.7, 169.4; **4s**: $\delta = 20.9$, 42.3, 57.6, 119.5, 119.7, 126.9, 128.4, 129.0, 129.2, 129.6, 132.8, 136.8, 137.0, 141.0, 167.6. ^{13}C NMR (125 MHz) were recorded on a Bruker Avance DRX 500 spectrometer with TMS as an internal standard.