PAPER

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A simple and efficient synthesis of 2-imidazolin-2-ones

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We report on the reactions of diazenes **1** and **2** with 1,3-dicarbonyl compounds. The first step involves a regioselective attack of the diazene on the active methylene group, giving the Michael adducts **3** or **4**, and can be performed either in the presence of sodium acetate or DBN (1,5-diazabicyclo[4.3.0]non-5-ene). The Michael adducts underwent ring-closure leading to 2-imidazolidinones **5** or **6** which were isolated in some cases. We found that **5** or **6** easily eliminated water in the presence of an acid to give imidazolin-2-ones **7** or **8** as the final products. The rate-determining step of this last mentioned process depends on the stereochemistry at C4 and C5 of the initial 2-imidazolidinone. A one-pot procedure to produce **7** or **8** directly from the diazene and the appropriate dicarbonyl partner is also described.

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Introduction

The imidazole ring is of therapeutic interest as it is widely recognized to be an important pharmacophore.[1] Its activity is often connected to its hydrogen bond donor–acceptor capability[2] or with high affinity for the metals that are present in many protein-active sites.[3] These characteristics make imidazole derivatives attractive targets in organic synthesis. Imidazolin-2-ones represent an important part of the imidazole family that possess functional motifs found in biologically active molecules.

As a part of our continuing interest in hydrazides[4] and other N–N-containing compounds,[5] we recently described the $ZrCl_4$-mediated treatment of substituted aminocarbonyldiazenecarboxylates with 1,3-diketones or β-ketoesters leading to highly functionalized imidazolin-2-ones.[6] In some cases we noticed the formation of the corresponding Michael adducts as the initial products that were further transformed to imidazolin-2-ones in the final step. The overall process takes place under mild reaction conditions and is regioselective with respect to both partners.

Results and discussion

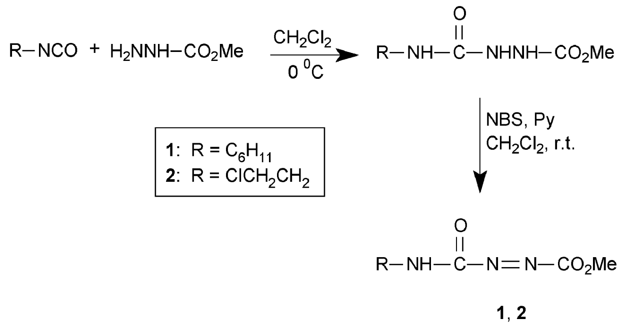
Here we report on a detailed investigation of the above-mentioned sequence and provide some additional evidence for the reaction pathway. Two alkyl aminocarbonyldiazenecarboxylates **1** and **2** were used in the present study. Both diazenes are easily produced by adding methyl carbazate to the appropriate isocyanate, followed by oxidation of the corresponding 1,4-disubstituted semicarbazide using NBS in pyridine (Scheme 1).

1,3-Diketones (**A**–**C**), β-ketoester (**D**) and β-ketoamides (**E**, **F**) were employed as 1,3-dicarbonyl partners. Although the reaction of a selected diazene with a 1,3-dicarbonyl compound could give two Michael adducts, due to the presence of two electrophilic nitrogens only one product was always observed, *i.e.*, the nitrogen atom adjacent to the amide functionality seems to be more electrophilic than the nitrogen attached to the ester group. The same regioselectivity was recently observed in studies that involved an electrophilic amination of aromatic substrates with similar diazenes.[7] Thus, a treatment of diazene **1** with 1,3-dicarbonyls **A**–**F** gave the Michael adducts **3a**–**3f** (Scheme 2).

Similar products were isolated on reaction of diazene **2** with selected 1,3-dicarbonyl partners which is demonstrated by the preparation of the adducts **4a**, **4e** and **4f**. The synthesis of any adduct requires an application of the appropriate catalyst. The best results were obtained using either sodium acetate or DBN (1,5-diazabicyclo[4.3.0]non-5-ene) as a promoter (Table 1).

The above Michael adducts **3** and **4** were isolated and fully characterized. Proton NMR spectra of most of the adducts exhibit a singlet for the enolic OH group in the range 14.5–16.4 ppm from TMS which is in agreement with the proposed structures.[8] This is not the case for **3b** and **3d**, which exist in solution in the diketo form. Although adducts are stable under neutral conditions at room temperature, ring closure to the corresponding 2-imidazolidinones **5** and **6** can occur in the presence of either an acid or a base. In most cases, 2-imidazolidinones **5** and **6** were not isolated, but they could be detected in crude reaction mixtures. They easily eliminate water in the presence of an acid to generate imidazolin-2-ones **7** and **8** in excellent yields (Table 2).

In contrast, 2-imidazolidinones were isolated when *N*-phenylacetoacetamide (**F**) was employed as a dicarbonyl partner. The reaction of diazene **1** with **F** in the presence of DBN led to a mixture of **5f′** and **5f″**. Similarly, the mixture of isomers **6f′** and **6f″** was obtained by the treatment of the diazene **1** with the same ketoamide. The products **5f′** and **6f′** were the predominant diastereoisomers, probably due to hydrogen bond formation between the enolic OH group and the neighbouring amido moiety. Each of the above mixtures was easily transformed to the corresponding imidazolin-2-one in methanolic solution in the presence of the ion-exchange resin Dowex® 50WX2-100. Therefore, imidazolin-2-one **7f** was prepared from the mixture of **5f′** and **5f″**, and the product **8f** was achieved from the mixture of **6f′** and **6f″**. A successful separation of both mixtures resulted in **5f′**, **5f″**, **6f′** and **6f″**, respectively, as diastereomerically pure isomers. The arrangement of the groups at C4 and C5 of the 2-imidazolidinone ring was supported by NOESY experiments, which showed a strong correlation between hydrogen at 4.15 ppm and OH at 6.60 ppm in the case of **5f″**, compared to a weak correlation between hydrogen at 3.95 ppm and OH at 6.13 ppm in **5f′**. Furthermore, a strong correlation



Scheme 1

between hydrogen at 4.25 ppm and OH at 6.74 ppm in 2-imidazolidinone **6f**″, and a weak correlation between hydrogen at 4.06 ppm and OH at 6.37 ppm in **6f**′, are also in agreement with the arrangement of the groups at C4 and C5. The structure of **5f**′ was also supported by X-ray analysis.[9]

The elimination of water, either from the mixture of **5f**′ and **5f**″ or from **6f**′ and **6f**″, was studied by ^{1}H NMR spectroscopy. Each mixture was dissolved in DMSO-d_6 and treated with 10 equivalents of CF_3CO_2D at 29 °C. The isomer **5f**″ disappeared from the reaction mixture within 26 min, whereas **5f**′ reacted completely after 48 min to give **7f** as the only product. Similarly, the isomer **6f**″ required 63 min, compared with 105 min for **6f**′ to produce **8f**. The above results indicate that the elimination of water from 2-imidazolidinone to obtain the final product depends on stereochemistry at C4 and C5. A plausible reaction pathway is depicted in Scheme 3.

It is well known that tertiary alcohols dehydrate in the presence of an acid by the E1 mechanism.[10] The first step, *i.e.*, the deuteration of the OH group, seems to be the rate-determining step for the entire process. Here, the deuteration of **5f**″ (or **6f**″) is obviously less hindered than that of **5f**′ (or **6f**′) which can result, after a smooth elimination of HOD, in a straightforward transformation of the corresponding carbocation. The latter is stabilized by the contribution of an acyliminium resonance structure due to the participation of the lone-pair of the adjacent nitrogen as shown in Scheme 3. Elimination of the proton from this carbocation leads to the final imidazolin-2-one **7f** (or **8f**). The fact that the intramolecular hydrogen bond between the tertiary OH group and the amido functionality is possible only in the case of **5f**′ (or **6f**′) is also in agreement with the faster elimination of HOD from **5f**″ (or **6f**″).

The isolation of Michael adducts **3** and **4**, as well as 2-imidazolidinones **5** and **6** can be avoided, as demonstrated by a one-pot synthesis of imidazolin-2-ones **7** or **8** from diazenes and the appropriate 1,3-dicarbonyl partners. The desired products were isolated in good to excellent yields (Table 3).

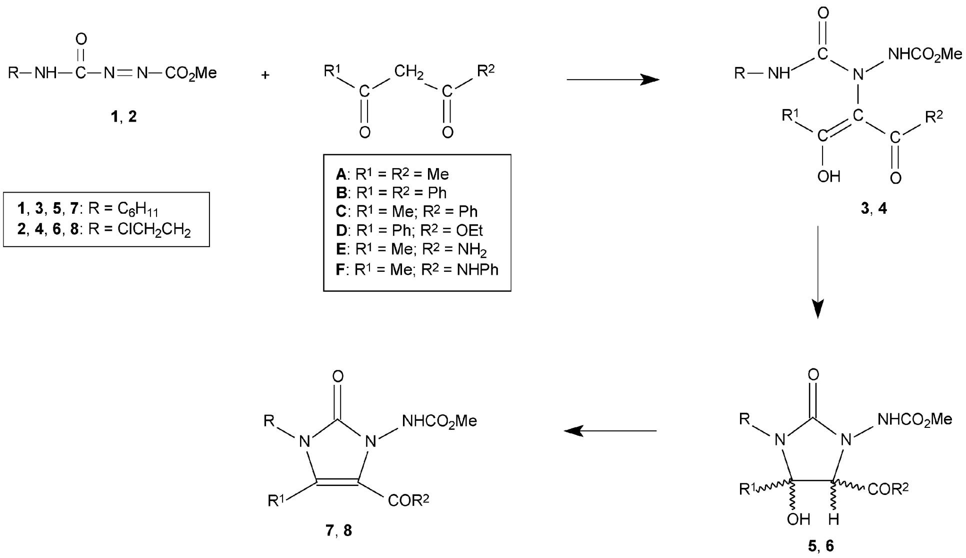
Conclusion

We have developed a new, simple and mild route to produce highly substituted imidazolin-2-ones. The initial steps which involve a regioselective addition of alkyl aminocarbonyldiazenecarboxylates **1** or **2** to the various 1,3-dicarbonyl compounds and further cyclization of Michael adducts into 2-imidazolidinones **5** and **6** take place either under basic or under acidic conditions. The dehydration of the 2-imidazolidinones to give the final products was carried out in the presence of an acid. The rate-determining step of the last process seems to depend on the steric hindrance around the tertiary OH group at position 4 in 2-imidazolidinones and on the formation of the hydrogen bond between this OH and the amide group at the vicinal position. It should be noted that an application of β-keto amides **E** and **F** in the above studies is particularly important from the point of view of the growing interest in various biologically active imidazole carboxamides[11] as our method offers a new, mild and direct route to these compounds. Furthermore, our method for the synthesis of 2-imidazolidinones may serve as a simple approach to various new chiral auxiliaries[12] and catalysts.[13]

Experimental

General methods

Melting points were determined on a Kofler micro hot stage and are uncorrected. IR spectra were measured as KBr pellets with a Bio-Rad FTS 3000MX spectrometer. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300.13 for ^{1}H NMR and 75.5 MHz for ^{13}C NMR, using TMS as the internal standard. Mass spectra were obtained on a VG-Analytical AutospecQ instrument. Elemental analyses (C, H, N) were performed on Perkin Elmer 2400 CHN Analyzer. TLC was carried out on Fluka silica gel TLC plates (F_{254}). Radial chromatography was carried out with a Harrison Research instrument, model 7924 T, employing Merck silica gel 60 PF_{254}. Dicarbonyl compounds **A**–**F** were purchased from commercial sources (Fluka, Merck, Aldrich) and used without further purification. The diazene **2** was prepared as described



Scheme 2

Table 1 The synthesis of Michael adducts

Reactants[a]	Promoter (mol%)	Reaction time/h	Product	Yield[b] (%)
1 + **A**	AcONa (10)	23	**3a**	78
1 + **B**	AcONa (10)	22	**3b**	95
1 + **C**	AcONa (20)	2	**3c**	96
1 + **D**	AcONa (20)	10[c]	**3d**	65[d]
1 + **E**	DBN (10)	1	**3e**	99
1 + **F**	AcONa (40)	5	**3f**	93
2 + **A**	AcONa (10)	4	**4a**	89
2 + **E**	DBN (10)	1	**4e**	92
2 + **F**	AcONa (10)	24	**4f**	91

[a] Reactions were carried out in CH_2Cl_2 at r.t.; THF was used as a solvent for **1** + **C**, ethyl acetate for **2** + **E**. [b] Isolated yields are given. [c] Under reflux. [d] After radial chromatography using petroleum ether–ethyl acetate (5 : 1).

Table 2 Ion-exchange resin-promoted cyclization of Michael adducts

Adduct[a]	Reaction time/h	Product	Yield[b] (%)
3a	18	**7a**	95
3b	13	**7b**	90
3c	17	**7c**	99
3d	4[c]	**7d**	100
3e	2	**7e**	99
3f	20	**7f**	100
4a	22	**8a**	100
4e	4.5	**8e**	100
4f	15.5	**8f**	100

[a] Reactions were carried out at r.t. in methanol in the presence of Dowex® 50WX2-100 (Aldrich; cat. No. 21744-1). [b] Isolated yields are given. [c] Under reflux.

earlier.[5a]. Petroleum ether corresponded to the fraction of bp 60–80 °C.

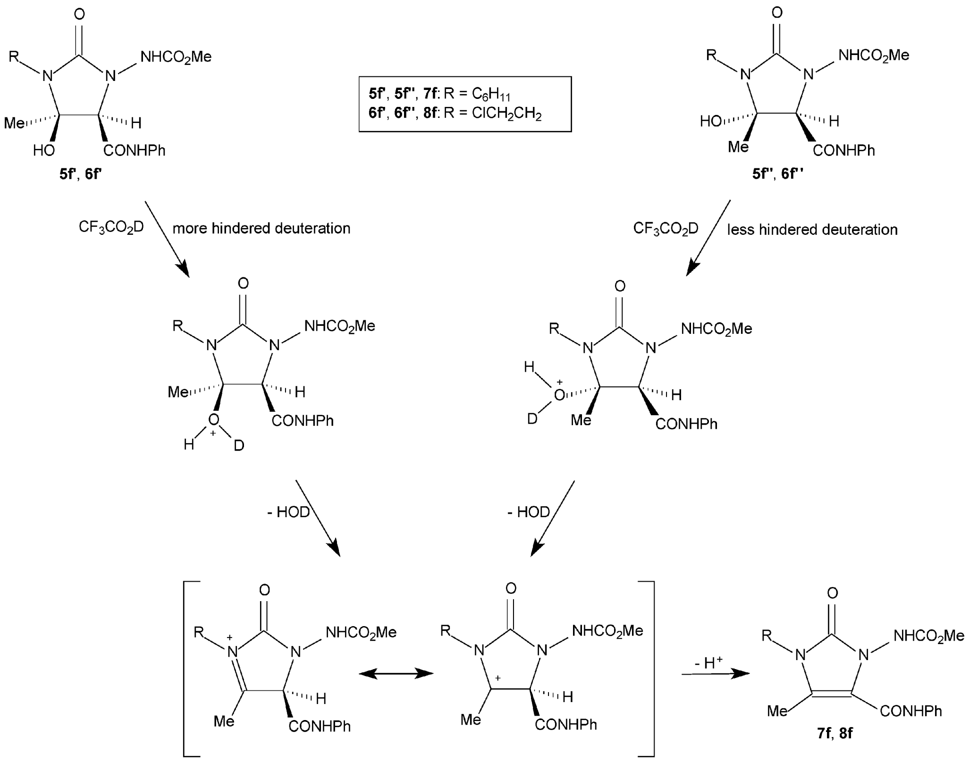
Synthesis of methyl cyclohexylaminocarbonyldiazenecarboxylate (1)

A solution of cyclohexyl isocyanate (629 mg, 5 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of methyl hydrazinecarboxylate (450 mg, 5 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for an additional 30 min. The solid material was filtered off and rinsed with diethyl ether (5 mL) to give methyl cyclohexylaminocarbonylhydrazinecarboxylate (969 mg, 90% yield): mp 144–145 °C (ethanol); IR (KBr): 3330, 3265, 2945, 1735, 1655, 1525, 1440, 1265, 1225, 1055 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.18 (m, 5H), 1.62 (m, 5H), 3.33 (m, 1H), 3.57 (s, 3H), 6.06 (d, $J = 9$ Hz, 1H), 7.53 (s, 1H), 8.71 (broad s, 1H); ^{13}C NMR (acetone-d_6): δ 26.5, 27.0, 34.8, 50.2, 53.2, 159.1, 159.2; MS (FAB) m/z (%) 216 ($M^+ + H$, 45), 91 (100). Anal. for $C_9H_{17}N_3O_3$ (215.25): calc.: C 50.22, H 7.96, N 19.52; found: C 50.05, H 8.06, N 19.33%.

NBS (587 mg, 3.25 mmol) was slowly added at room temperature to a stirred suspension of methyl cyclohexylaminocarbonylhydrazinecarboxylate (430 mg, 2 mmol) and pyridine (325 μL, 4 mmol) in dichloromethane (10 mL). After 30 min, the reaction mixture was treated with HCl (1 : 1, 10 mL) and two layers were separated. The dichloromethane solution was washed first with aqueous solution of $Na_2S_2O_3$ (5%, 10 mL), then with a saturated solution of $NaHCO_3$ (10 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness to achieve the diazene **1** (388 mg, 91% yield): mp 48–50 °C (petroleum ether–toluene); IR (KBr): 3298, 2934, 2856, 1771, 1709, 1557, 1523, 1437, 1260, 1229 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.15–1.33 (m, 5H), 1.56–1.86 (m, 5H), 3.56 (m, 1H), 4.02 (s, 3H), 9.03 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 24.4, 25.0, 32.2, 50.2, 55.1, 157.8, 161.9; MS (FAB) m/z (%) 214 ($M^+ + H$, 100), 90 (18), 83 (24), 55 (10). Anal. for $C_9H_{15}N_3O_3$ (213.23): calc.: C 50.69, H 7.09, N 19.71; found: C 51.00; H 7.20, N 19.79%.

Preparation of Michael adducts

Typical procedure. Methyl cyclohexylaminocarbonyldiazenecarboxylate (**1**, 213 mg, 1 mmol) was slowly added at room



Scheme 3

Table 3 A one-pot synthesis of 2-imidazolin-2-ones from diazenes and 1,3-dicarbonyl compounds

Reactants	Promoter[a]	Reaction time/h	Method	Product	Yield[b] (%)
1 + **A**	$ZrCl_4$; Dowex	4;[c] 17[d]	II	**7a**	86
1 + **B**	$ZrCl_4$; Dowex	4;[c] 13[d]	II	**7b**	90
1 + **C**	CF_3COOH[e]	18	III	**7c**	87
1 + **D**	$ZrCl_4$; Dowex[f]	2;[c] 3[d]	II	**7d**	92
1 + **E**	CF_3COOH	120	III	**7e**	86
1 + **F**	AcONa; Dowex	7;[c] 20[d]	IV	**7f**	94
2 + **A**	$ZrCl_4$; Dowex	4;[c] 13[d]	II	**8a**	73
2 + **B**	$ZrCl_4$	10	I	**8b**	93
2 + **C**	CF_3COOH	18	III	**8c**	83
2 + **D**	AcONa[f]; Dowex	2;[c] 96[d]	IV	**8d**	84
2 + **E**	AcONa; Dowex	10	IV	**8e**	78
2 + **F**	AcONa; Dowex	2;[c] 48[d]	IV	**8f**	83

[a] Reactions were carried out at r.t. unless stated otherwise. [b] Isolated yields are given. [c] Reaction time for treatment of the reaction mixture with the first promoter. [d] Reaction time required for the second promoter that was applied after the first one to give the final product. [e] At 0 °C. [f] Under reflux.

temperature to a stirred suspension of dibenzoylmethane (**B**, 224 mg, 1 mmol) and sodium acetate (8.2 mg, 0.1 mmol) in dichloromethane (6 mL). Stirring was continued for 22 h, the reaction mixture was then evaporated to dryness, the residue was washed with water (10 mL) and diethyl ether (10 mL) to produce the adduct **3b** (415 mg; 95% yield). Other details for the synthesis of adducts **3** and **4** are given in Table 1.

Methyl 2-(1-acetyl-2-hydroxypropen-1-yl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3a). Mp 136.8–140 °C (ethyl acetate); IR (KBr): 3360, 3222, 1727, 1661, 1630, 1558, 1519, 1449, 1259,1205 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.18 (m, 1H), 1.24 (m, 4H), 1.55 (m, 1H), 1.67 (m, 4H), 2.14 (s, 6H), 3.39 (m, 1H), 3.60 (s, 3H), 6.55 (s, 1H), 9.38 (s, 1H), 16.09 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 22.1, 25.1, 25.2, 32.8, 49.6, 51.9, 78.5, 117.7, 155.2, 192.8; MS (FAB) m/z (%) 314 (M^+ + H, 100), 189 (65), 114 (77), 76 (43). Anal. for $C_{14}H_{23}N_3O_5$ (313.35): calc.: C 53.66, H 7.40, N 13.41; found: C 53.93, H 7.46, N 13.35%.

Methyl 2-(1-benzoyl-2-oxo-2-phenylethyl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3b). Mp 191–194 °C (methanol –DMF); IR (KBr): 3340, 3311, 2930, 2854, 1755, 1695, 1668, 1597, 1536, 1449, 1440, 1270, 1247 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.01–1.24 (m, 5H), 1.52–1.66 (m, 5H), 3.37 (m, 1H), 3.63 (s, 3H), 6.72 (d, J = 7.7 Hz, 1H), 7.10 (broad s, 1H), 7.16 (s, 1H), 7.52 (m, 4H), 7.65 (m, 2H), 8.02 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 24.1, 25.1, 32.6, 47.6, 53.6, 69.4, 128.66, 128.70, 133.8, 135.1, 156.1, 156.9, 193.3; MS (EI) m/z (%) 437 (M^+, 0.4), 312 (14), 105 (100), 77 (51). Anal. for $C_{24}H_{27}N_3O_5$ (437.49): calc.: C 65.89, H 6.22, N 9.60; found: C 65.89, H 6.41, N 9.46%.

Methyl 2-(1-benzoyl-2-hydroxypropen-1-yl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3c). Mp 116–120 °C (diethyl ether); IR (KBr): 3348, 3297, 2931, 2856, 1761, 1661, 1602, 1530, 1451, 1331, 1235, 1099 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07–1.24 (m, 3H), 1.31–1.49 (m, 2H), 1.63–1.80 (m, 3H), 1.92–2.06 (m, 2H), 2.47 (s, 3H), 3.64–3.78 (m, 1H), 3.67 (s, 3H), 5.19 (broad, 1H), 5.71 (broad s, 1H), 7.42–7.58 (m, 5H), 16.36 (broad s, 1H); MS (FAB) m/z (%) 376 (M^+ + H, 77), 251 (100), 176 (64), 105 (85). Anal. for $C_{19}H_{25}N_3O_5 \cdot 0.4\ Et_2O$: calc.: C 61.08, H 7.22, N 10.37; found: C 61.20, H 7.44, N 10.43%.

Methyl 2-(1-benzoyl-2-ethoxy-2-oxoethyl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3d). Mp 104–108.3 °C (petroleum ether–ethyl acetate); IR (KBr): 3320, 2930, 1760, 1735, 1665, 1644, 1520, 1235, 1210, 1184 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.17 (t, J = 7.1 Hz, 3H), 1.19 (m, 5H), 1.58 (m, 5H), 3.36 (m, 1H), 3.55 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 6.11 (broad s, 1H), 6.68 (d, J = 8.1 Hz, 1H), 7.52 (m, 2H), 7.65 (m, 1H), 8.02 (m, 2H), 8.89 (broad s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.8, 24.8, 25.1, 32.5, 32.6, 49.5, 52.0, 61.2, 128.3, 128.5, 133.4, 135.5, 155.8, 156.1, 167.0, 190.5; MS (FAB) m/z (%) 406 (M^+ + H, 100), 281 (66), 105 (67), 55 (56). Anal. for $C_{20}H_{27}N_3O_6$ (405.45): calc.: C 59.25, H 6.71, N 10.36; found: C 59.15, H 6.49, N 10.44%.

Methyl 2-(1-aminocarbonyl-2-hydroxypropen-1-yl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3e). Mp 142–147 °C (petroleum ether–ethyl acetate); IR (KBr): 3377, 3204, 2855, 1733, 1665, 1531, 1451, 1329, 1252, 998 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.05 (m, 1H), 1.21 (m, 4H), 1.60 (m, 5H), 1.88 (s, 3H), 3.37 (m, 1H), 3.64 (s, 3H), 6.40 (d, J = 8.1 Hz, 1H), 7.50 (s, 1H), 7.73 (s, 1H), 9.47 (s, 1H), 15.42 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 18.1, 25.1, 25.2, 32.7, 49.6, 52.3, 106.9, 155.0, 158.8, 173.2, 176.0; MS (FAB) m/z (%) 315 (M^+ + H, 90), 190 (98), 185 (63), 93 (100). Anal. for $C_{13}H_{22}N_4O_5$ (314.34): calc.: C 49.67, H 7.05, N 17.82; found: C 49.42, H 7.21, N 17.53%.

Methyl 2-(1-anilinocarbonyl-2-hydroxypropen-1-yl)-2-(cyclohexylaminocarbonyl)hydrazinecarboxylate (3f). Mp 173–176 °C (ethyl acetate–methanol); IR (KBr): 3350, 3196, 2937, 1732, 1659, 1629, 1556, 1489, 1446, 1252, 901 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.04 (m, 1H), 1.21 (m, 4H), 1.60 (m, 5H), 1.94 (s, 3H), 3.37 (m, 1H), 3.71 (s, 3H), 6.73 (d, J = 8.1 Hz, 1H), 7.10 (m, 1H), 7.33 (m, 2H), 7.45 (m, 2H), 9.82 (s, 1H), 10.27 (s, 1H), 14.51 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 25.0, 25.7, 29.8, 31.0, 51.2, 52.3, 71.0, 84.4, 119.3, 123.7, 128.7, 138.1, 157.0, 157.1, 165.0; MS (FAB) m/z (%) 391 (M^+ + H, 30), 298 (43), 266 (68), 174 (72), 55 (100). Anal. for $C_{19}H_{26}N_4O_5$ (390.43): calc.: C 58.45, H 6.71, N 14.35; found: C 58.44, H 6.69, N 14.55%.

Methyl 2-(1-acetyl-2-hydroxypropen-1-yl)-2-(2-chloroethylaminocarbonyl)hydrazinecarboxylate (4a). Mp 167.2–171.5 °C (petroleum ether–ethyl acetate); IR (KBr): 3400, 3251, 1749, 1670, 1531, 1244 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.18 (s, 6H), 3.34 (m, 2H), 3.60 (m, 2H), 3.61 (s, 3H), 7.15 (s, 1H), 9.51 (s, 1H), 16.16 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 22.1, 42.2, 43.5, 51.9, 78.5, 117.5, 155.9, 193.1; MS (FAB) m/z (%) 294 (M^+ + H, 14), 189 (13), 71 (99), 55 (100). Anal. for $C_{10}H_{16}ClN_3O_5$ (293.70): calc.: C 40.89, H 5.49, N 14.31; found: C 40.64, H 5.53, N 14.09%.

Methyl 2-(1-aminocarbonyl-2-hydroxypropen-1-yl)-2-(2-chloroethylaminocarbonyl)hydrazinecarboxylate (4e). Mp 205–207 °C (methanol); IR (KBr): 3347, 3252, 1732, 1668, 1630, 1559, 1526, 1445, 1325, 1256 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 1.92 (s, 3H), 3.36 (m, 2H), 3.57 (m, 2H), 3.65 (s, 3H), 7.03 (s, 1H), 7.57 (s, 1H), 7.78 (s, 1H), 9.61 (s, 1H), 15.52 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 18.2, 42.2, 43.3, 52.4, 106.6, 155.6, 158.9, 173.1, 176.6; MS (FAB) *m*/*z* (%) 295 (M$^+$ + H, 30), 154 (58), 71 (75), 55 (100). Anal. for $C_9H_{15}ClN_4O_5$ (294.69): calc.: C 36.68, H 5.13, N 19.01; found: C 36.60, H 5.03, N 18.78%.

Methyl 2-(1-anilinocarbonyl-2-hydroxypropen-1-yl)-2-(2-chloroethylaminocarbonyl)hydrazinecarboxylate (4f). Mp 157–162 °C (dichloromethane–methanol); IR (KBr): 3345, 3196, 1730, 1665, 1628, 1597, 1561, 1524, 1450, 1328, 1256 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 2.00 (s, 3H), 3.38 (m, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 7.11 (m, 1H), 7.36 (m, 3H), 7.57 (m, 2H), 9.96 (s, 1H), 10.33 (s, 1H), 14.61 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 18.3, 42.3, 43.5, 52.9, 107.8, 119.7, 124.0, 128.9, 137.7, 155.7, 159.9, 168.9, 176.6; MS (EI) *m*/*z* (%) 370 (M$^+$, 7), 291 (14), 222 (68), 93 (100). Anal. for $C_{15}H_{19}ClN_4O_5$ (370.79): calc.: C 48.59, H 5.16, N 15.11; found: C 48.71, H 5.29, N 15.02%.

Formation of 2-imidazolidinones

Isomers 5f′ and 5f″. The diazene **1** (319.8 mg, 1.5 mmol) was slowly added to the solution of *N*-phenylacetoacetamide (265.5 mg, 1.5 mmol) and DBN (18.7 mg, 0.15 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 1.5 h and evaporated to dryness. The residue was purified by radial chromatography using petroleum ether–ethyl acetate (5 : 2) to give 410 mg of **5f′** (70% yield), 40 mg of **5f″** (4% yield) and 57 mg of the adduct **3f** (10% yield).

5f′. Mp 140–143.5 °C (petroleum ether–ethyl acetate); IR (KBr): 3267, 2937, 2854, 1749, 1726, 1682, 1599, 1549, 1493, 1446, 1375, 1319, 1271, 1258, 764 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 1.16 (m, 3H), 1.58 (s, 3H), 1.68 (m, 5H), 2.02 (m, 2H), 3.14 (m, 1H), 3.64 (s, 3H), 3.95 (s, 1H), 6.13 (s, 1H), 7.08 (m, 1H), 7.33 (m, 2H), 7.64 (m, 2H), 9.29 (s, 1H), 9.45 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 25.0, 25.5, 29.7, 31.0, 51.2, 52.3, 70.9, 84.4, 119.3, 123.7, 128.7, 138.1, 157.0, 157.1, 164.9; MS (FAB) *m*/*z* (%)391 (M$^+$ + H, 32), 373 (100), 280 (27), 254 (92), 172 (40). Anal. for $C_{19}H_{26}N_4O_5 \cdot 0.6$ EtOAc: calc.: C 57.98, H 7.00, N 12.64; found: C 58.23, H 7.01, N 12.49%.

5f″. Mp 137–140 °C (diethyl ether); IR (KBr): 3328, 2926, 2855, 1732, 1700, 1678, 1602, 1555, 1502, 1445, 1259, 1250, 757 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 1.04–1.31 (m, 3H), 1.32 (s, 3H), 1.52–1.76 (m, 5H), 2.04 (m, 2H), 3.10 (m, 1H), 3.63 (s, 3H), 4.15 (s, 1H), 6.59 (s, 1H), 7.11 (m, 1H), 7.33 (m, 2H), 7.64 (m, 2H), 9.35 (s, 1H), 9.82 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 22.1, 25.0, 25.7, 25.8, 29.6, 30.8, 50.5, 52.2, 72.5, 85.0, 119.7, 123.9, 128.7, 138.0, 155.3, 157.1, 165.9; MS (EI) *m*/*z* (%) 390 (M$^+$, 1.1), 372 (79), 215 (23), 197 (33), 93 (86), 55 (100); MS (FAB) *m*/*z* (%) 391 (M$^+$ + H, 9.2), 373 (6.6), 154 (80), 136 (66), 69 (60), 55 (100); HRMS for $C_{19}H_{26}N_4O_5$: calc.: 390.1903; found: 390.1913. Anal. for $C_{19}H_{26}N_4O_5$: calc.: C 58.45, H 6.71, N 14.35; found: C 58.31, H 6.81, N 14.23%.

Isomers 6f′ and 6f″. The diazene **2** (290.3 mg, 1.5 mmol) was slowly added to the solution of *N*-phenylacetoacetamide (265.5 mg, 1.5 mmol) and DBN (18.7 mg, 0.15 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 2 h. Dichloromethane (15 mL) was added to the reaction mixture at 30 °C and then the solution was treated successively with 5% HCl (1.5 mL) and water (1.5 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by radial chromatography using petroleum ether–ethyl acetate (5 : 3) to give 293.7 mg of **6f′** (53% yield), 140.9 mg of **6f″** (25% yield) and 65.4 mg of the adduct **4f** (12% yield).

6f′. Mp 150–155 °C (dichloromethane–methanol); IR (KBr): 3327, 3236, 1733, 1723, 1664, 1600, 1549, 1453, 1437, 1410, 1265 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 1.60 (s, 3H), 3.46 (m, 2H), 3.65 (s, 3H), 3.71 (m, 2H), 4.06 (s, 1H), 6.37 (s, 1H), 7.09 (m, 1H), 7.34 (m, 2H), 7.64 (m, 2H), 9.49 (s, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 25.6, 41.2, 41.8, 52.5, 70.7, 83.9, 119.3, 123.8, 128.7, 138.1, 157.0, 158.2, 164.5; MS (EI) *m*/*z* (%) 370 (M$^+$, 2), 352 (94), 228 (64), 93 (100), 63 (65); HRMS for $C_{15}H_{19}ClN_4O_5$: calc.: 370.1044; found: 370.1055. Anal. for $C_{15}H_{19}ClN_4O_5$: calc.: C 48.59, H 5.16, N 15.11; found: C 48.84, H 5.31, N 14.96%.

6f″. Mp 109–113 °C (dichloromethane); IR (KBr): 3359, 3316, 3212, 1749, 1721, 1707, 1651, 1601, 1539, 1488, 1437, 1229 cm^{-1}; ^{1}H NMR (DMSO-*d*$_6$): δ 1.39 (s, 3H), 3.44 (m, 2H), 3.63 (s, 3H), 3.67 (m, 2H), 4.25 (s, 1H), 6.74 (s, 1H), 7.10 (m, 1H), 7.34 (m, 2H), 7.64 (m, 2H), 9.47 (s, 1H), 9.99 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$): δ 22.1, 40.7, 41.6, 52.3, 72.1, 84.7, 119.7, 124.0, 128.8, 138.0, 156.6, 156.7, 165.6; MS (EI) *m*/*z* (%) 370 (M$^+$, 2), 352 (93), 228 (70), 93 (100), 63 (65); HRMS for $C_{15}H_{19}ClN_4O_5$: calc.: 370.1044; found: 370.1053. Anal. for $C_{15}H_{19}ClN_4O_5 \cdot 0.75H_2O$: calc.: C 46.88, H 5.38, N 14.58; found: C 46.67, H 5.60, N 14.43%.

Cyclization of Michael adducts

An ion-exchange resin Dowex® 50WX2-100 (Aldrich; cat. No. 21744-1; 650 mg) was added to the selected adduct (0.25 mmol) in methanol (5 mL) and the reaction mixture was stirred at room temperature for 2–22 h (see Table 2 for details). The resin was filtered off and the filtrate was evaporated to dryness to produce the corresponding imidazolin-2-one **7** or **8** with an excellent yield.

One-pot procedure for the preparation of imidazolin-2-ones 7 and 8

The reactions of diazenes (**1**, **2**) with various 1,3-dicarbonyl compound (**A**–**F**) were carried out using the appropriate (see Table 3) method described below, which led to the formation of imidazolin-2-ones **7** or **8**.

Method I. A solution of the diazene **2** (213 mg, 1.1 mmol) and dibenzoylmethane (**B**, 224.3 mg, 1 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a stirred suspension of $ZrCl_4$ (1.1 mmol) in CH_2Cl_2 (5 mL) at 20 °C under argon. The reaction mixture was stirred at the same temperature for 10 h, quenched with water (5 mL) and neutralized with saturated aqueous $NaHCO_3$. The two phases were separated, and the aqueous solution was extracted with CH_2Cl_2 (4 × 10 mL). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness to give **8b** (372.1 mg, 93%).

Method II. The diazene **1** (352 mg, 1.65 mmol) and dibenzoylmethane (336.5 mg, 1.5 mmol) reacted in the presence of $ZrCl_4$ (385 mg, 1.65 mmol) as described in method I (reaction time: 4 h). The residue, obtained after the evaporation of the combined CH_2Cl_2 extracts, was treated with the ion-exchange resin Dowex® 50WX2-100 (200 mg) in methanol (10 mL) for 13 h at room temperature. Next, the resin was filtered off and the filtrate was evaporated to dryness to produce 568.5 mg of **7b** (90% yield).

Method III. A mixture of acetoacetamide (**E**, 151.7 mg, 1.5 mmol), diazene **1** (319.8 mg, 1.5 mmol) and trifluoroacetic acid (1.53 mL, 20 mmol) in dichloromethane (10 mL) was stirred at room temperature for 120 h. The reaction mixture was evaporated to dryness, dissolved in dichloromethane (10 mL) and treated successively with saturated $NaHCO_3$ (5 mL) and with water (2 × 7 mL). The dichloromethane solution was dried over anhydrous Na_2SO_4 and evaporated to dryness to give **7e** (384.8 mg, 86% yield).

Method IV. A mixture of the diazene **1** (213.2 mg, 1 mmol), *N*-phenylacetoacetamide (**F**, 177 mg, 1 mmol) and sodium acetate (35.2 mg, 0.4 mmol) in dichloromethane (5 mL) was stirred at room temperature for 7 h. Next, dichloromethane was added (10 mL) and the mixture was washed with water (7 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was dissolved in methanol (7 mL), an ion-exchange resin was added (250 mg) and the reaction mixture was stirred for 20 h at room temperature. The resin was filtered off and the filtrate evaporated to dryness to give the product **7f** (353.7 mg, 94% yield).

Characterization of imidazolin-2-ones 7 and 8

Methyl 5-acetyl-3-cyclohexyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (7a) and methyl 5-benzoyl-3-cyclohexyl-2-oxo-4-phenyl-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (7b). See ref. 6.

Methyl 5-benzoyl-3-cyclohexyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (7c). Mp 169.8–172.0 °C (petroleum ether–ethyl acetate); IR (KBr): 3150, 2910, 1750, 1690, 1560, 1250 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.15 (m, 1H), 1.32 (m, 2H), 1.62 (m, 1H), 1.76 (m, 4H), 1.96 (s, 3H), 2.16 (m, 2H), 3.56 (s, 3H), 3.77 (m, 1H), 7.50 (m, 2H), 7.62 (m, 3H), 9.89 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 11.1, 24.7, 25.3, 29.2, 52.2, 53.8, 119.2, 128.5, 128.6, 129.8, 132.4, 138.9, 151.0, 155.7, 183.6; MS (FAB) m/z (%) 358 ($M^+ + H$, 100), 275 (11), 201 (10), 105 (64). Anal. for $C_{19}H_{23}N_3O_4$ (357.40): calc.: C 63.85, H 6.49, N 11.76; found: C 64.19, H 6.44, N 11.72%.

Ethyl 1-cyclohexyl-3-(methoxycarbonylamino)-2-oxo-5-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxylate (7d). See ref. 6.

Methyl 5-aminocarbonyl-3-cyclohexyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (7e). Mp 207–210 °C (ethyl acetate–methanol); IR (KBr): 3185, 2928, 1742, 1698, 1665, 1585, 1450, 1316, 1224, 1079 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.14 (m, 1H), 1.31 (m, 2H), 1.64 (m, 3H), 1.77 (m, 2H), 2.10 (m, 2H), 2.31 (s, 3H), 3.64 (s, 3H), 3.73 (m, 1H), 7.06 (broad d, 2H), 9.79 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 9.8, 24.7, 25.4, 29.5, 52.5, 53.2, 113.8, 124.6, 150.8, 155.9, 160.2; MS (EI) m/z (%) 296 (M^+, 80), 214 (82), 197 (99), 169 (73), 140 (100), 55 (89). Anal. for $C_{13}H_{20}N_4O_4$ (296.32): calc.: C 52.69, H 6.80, N 18.91; found: C 52.81, H 6.92, N 18.70%.

Methyl 5-anilinocarbonyl-3-cyclohexyl-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (7f). Mp 182–183.5 °C (petroleum ether–ethyl acetate); IR (KBr): 3334, 2932, 1742, 1697, 1661, 1599, 1538, 1397, 1442, 1249, 758 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.16 (m, 1H), 1.34 (m, 2H), 1.65 (m, 3H), 1.79 (m, 2H), 2.14 (m, 2H), 2.29 (s, 3H), 3.62 (s, 3H), 3.78 (m, 1H), 7.07 (m, 1H), 7.31 (m, 2H), 7.60 (m, 2H), 9.74 (s, 1H), 9.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 10.3, 24.7, 25.4, 29.5, 52.5, 53.4, 115.0, 119.4, 123.5, 123.7, 128.7, 138.7, 150.8, 155.9, 156.9; MS (EI) m/z (%) 372 (M^+, 65), 215 (43), 197 (57), 93 (100), 55 (56). Anal. for $C_{19}H_{24}N_4O_4$ (372.42): calc.: C 61.28, H 6.50, N 15.04; found: C 61.56, H 6.41, N 14.81%.

Methyl 5-acetyl-3-(2-chloroethyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (8a), methyl 5-benzoyl-3-(2-chloroethyl)-2-oxo-4-phenyl-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (8b), methyl 5-benzoyl-3-(2-chloroethyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (8c) and ethyl 1-(2-chloroethyl)-3-methoxycarbonylamino-2-oxo-5-phenyl-2,3-dihydro-1*H*-imidazole-4-carboxylate (8d). See ref. 6.

Methyl 5-aminocarbonyl-3-(2-chloroethyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (8e). Mp 215–218 °C (ethyl acetate–methanol); IR (KBr): 3411, 3208, 1753, 1686, 1658, 1587, 1522, 1447, 1400, 1378, 1341, 1250 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.33 (s, 3H), 3.66 (broad, 3H), 3.81 (t, J = 5.9 Hz, 2H), 3.95 (t, J = 5.9 Hz, 2H), 7.12 (broad, 2H), 9.92 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 9.6, 42.0, 42.3, 52.6, 114.0, 124.8, 151.2, 155.8, 160.0; MS (EI) m/z (%) 276 (M^+, 35), 217 (14), 202 (100), 185 (15), 152 (79). Anal. for $C_9H_{13}ClN_4O_4$ (276.68): calc.: C 39.07, H 4.74, N 20.25; found: C 39.20, H 4.88, N 19.95%.

Methyl 5-anilinocarbonyl-3-(2-chloroethyl)-4-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-1-ylcarbamate (8f). Mp 152–154 °C (petroleum ether–ethyl acetate); IR (KBr): 3308, 3241, 1740, 1712, 1654, 1526, 1445, 1410, 1281, 756 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.32 (s, 3H), 3.63 (s, 3H), 3.84 (t, J = 6.1 Hz, 2H), 4.00 (t, J = 6.1 Hz, 2H), 7.08 (m, 1H), 7.32 (m, 2H), 7.61 (m, 2H), 9.78 (s, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 10.0, 42.0, 42.5, 52.5, 115.0, 119.6, 123.6, 124.0, 128.7, 138.6, 151.2, 155.8, 156.7; MS (FAB) m/z (%) 353 ($M^+ + H$, 20), 260 (10), 135 (70), 71 (55), 55 (62). Anal. for $C_{15}H_{17}ClN_4O_4$ (352.77): calc.: C 51.07, H 4.86, N 15.88; found: C 51.09, H 5.06, N 15.77%.

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