A novel acid-catalyzed rearrangement of 2-substituted-3-(2-nitrophenyl)oxiranes for the synthesis of di- and mono-oxalamides†

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Introduction

Oxiranes are one of the most versatile classes of organic compounds available to the synthetic chemist.1 They can be prepared by a wide variety of methods.2 One of the most frequently used atom economical reactions of oxiranes is their rearrangement to carbonyl compounds, and a number of reagents including a variety of Lewis acids3 have been elaborated for this purpose. In principle, for trisubstituted oxiranes two types of rearrangements are possible depending on the migration pathways following the Lewis acid promoted C-O bond cleavage (Scheme 1). The rearrangement of I with hydride (path a) or the alkyl/aryl migration (path b) would lead to ketone II or aldehyde III, respectively.3-4 The synthetic applications of oxiranes have been the subject of a number of reviews.4,5

The promise of increased chemo-, regio-, and stereoselectivity available via transition metal catalysis6 has led investigators to study the interactions of oxiranes with transition metal complexes, and a number of interesting and useful isomerization reactions have been reported. Notably, oxiranes activated by adjacent aryl, vinyl, silyl, or carbonyl substituents are isomerized to carbonyl compounds or allylic alcohols by complexes of Rh,7 Pd,8 Mo,9 Sm,10 Fe11 and In.12

Unlike all the considered reactions proceeding depending on the structure of oxirane and applied conditions of rearrangement on the path a or b, our strategy included the use of oxiranes, containing substituents with functional groups instead of the usual alkyl or aryl substituents. These functional groups promote an intramolecular condensation (cyclization) of intermediate ketone II or aldehyde III formed as a result of the above two transformations. Recently, our group reported a novel metal-free transannulation reaction of N3-diaryloxirane-2-carboxamides (AOCAs) involving a one-pot acid-catalyzed Meinwald rearrangement and intramolecular Friedel-Crafts alkylation processes allowing to synthesize various 3-
arylquinolin-2(1H)-ones in high yields (Scheme 2). This novel approach features not only a metal-free bond formation but also an exclusive 1,2-aryl migration.

During our studies on the ring-opening/ring-closure reactions of AOCAs, we attempted to use N-aryl-3-(2-nitroaryl) oxirane-2-carboxamides (obtained from 2-nitrobenzaldehydes and 2-chloro-N-arylacetamides) with the aim of expanding the scope of the reaction. We found that compounds with a newly formed oxalamide chain were obtained instead of expected 3-(2-nitroaryl)quinolin-2(1H)-ones when the reactions were carried out in refluxing AcOH in the presence of H2SO4. As far as we know, there has been no report on the synthesis of unsymmetric oxalamides via the rearrangement yet. Herein, we report this novel acid-catalyzed rearrangement of AOCAs in AcOH, which proceeds through a cascade of the ring-opening/ring-closure/ring-opening/ring-opening processes.

The salient features of our method are as follows: (1) a variety of aldehydes 1 and chloroacetamides 2 are readily available and the rapid synthesis of 3 with diverse substitution patterns are possible; (2) only two steps are necessary beginning with the starting materials to the products 4; (3) the facile isolation of 3 and 4 are accomplished by a simple aqueous workup.

### Results and discussion

The procedure of the Darzens condensation is the same as that described for AOCAs, except that only 2-nitrobenzaldehydes instead of variously substituted aromatic aldehydes with chloroacetamides were used and the reactions were carried out at room temperature for 7 h. The mixtures of cis- and trans-isomers of 3-(2-nitroaryl)oxirane-2-carboxamides (3) with the predominance of the trans-isomer were easily purified from the cis-isomer by washing with ether (Table 1).

The structures of 3a-h were proved by variety of 1D/2D NMR correlation methods (see ESI†). First of all to clarify the optimal reaction conditions we examined the rearrangement of trans-3-(2-nitrophenyl)oxirane-2-carboxamide (3a). After a brief survey of the reaction conditions, we have found that the product 4a is obtained in almost quantitative yield at reflux for 3 h in AcOH with 1 equiv. of H2SO4 (Table 2, entry 1). The reflux of 3a in both MeCN (with 1 equiv. H2SO4) and AcOH for 3 h resulted in the mixtures containing 30 and 10% (determined by 1H NMR) of the desired product 4a, respectively. Further optimization of the reaction conditions was carried out with trans-3-(2-nitrophenyl)oxirane-2-carboxamide (3h). The reflux of 3h in H2O with 1 equiv. H2SO4 for 5 h or its storage at room temp in AcOH with 1 equiv. of H2SO4 for 24 h gave 57% by refluxing 3h in AcOH with 1 equiv. of H2SO4 for 3 h at 0–15 °C by reacting chloroacetyl chloride with an equimolar amounts of corresponding aniline and Et3N. The compounds 2a and 2g are commercially available. a Ratio was determined by 1H NMR of the crude products. Yields refer to isolated trans-isomers of 3. c cis-Isomer of this compound was obtained early.¹³

### Table 1 Synthesis of 3-(2-nitroaryl)oxiran-2-carboxamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>Product</th>
<th>Yield&lt;sup&gt;trans&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt; (%)</th>
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<tr>
<td>1</td>
<td>1a H 2a Ph</td>
<td>3a&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
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</table>

<sup>a</sup> 2-Chloro-N-arylacetamides 2b-f were obtained on a 0.1 mol scale at 0–15 °C by reacting chloroacetyl chloride with an equimolar amounts of corresponding aniline and Et3N. The compounds 2a and 2g are commercially available. b Ratio was determined by 1H NMR of the crude products. c Yields refer to isolated trans-isomers of 3. d cis-Isomer of this compound was obtained early.

### Table 2 Synthesis of N-(2-carboxyaryl)oxalamides

<table>
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<tr>
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<tr>
<td>2</td>
<td>3b H 4-BrC6H4</td>
<td>4b</td>
<td>100</td>
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<tr>
<td>3</td>
<td>3c H 3-MeC6H4</td>
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<td>4</td>
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<td>3e H 3-NO2C6H4</td>
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<td>6</td>
<td>3f H 4-CO2EtC6H4</td>
<td>4f</td>
<td>97</td>
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<tr>
<td>7</td>
<td>3g 5-Cl Ph</td>
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<tr>
<td>8</td>
<td>3h H H</td>
<td>4h</td>
<td>97</td>
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</table>

<sup>a</sup> Yields refer to isolated products.
ester group (entry 6) is not subjected to hydrolysis and it can be used in further transformations. The presence of the chlorine atom with the −I and +M electronic effects in the aldehyde component does not influence the yield of the rearrangement product (entry 7).

To our delight 3-(2-nitrophenyl)oxirane-2-carboxamides undergo the rearrangement with the formation of compounds which can be considered both as anthranilic acid and as unsymmetrical oxalamide derivatives. Anthranilic acid derivatives are potential anticancer agents\textsuperscript{16} and the ligands for farnesoid X receptor.\textsuperscript{17} Oxalamides also represent a key framework of many bioactive compounds.\textsuperscript{18} They have been developed as acetylcholine esterase inhibitors,\textsuperscript{19} C5a inhibitors,\textsuperscript{20} nitric oxide synthase inhibitors,\textsuperscript{21} anti-HIV agents,\textsuperscript{22} antiepileptic drugs,\textsuperscript{23} HIV integrase inhibitors,\textsuperscript{24} HIV-1 protease inhibitors,\textsuperscript{25} cephalosporin bactericides\textsuperscript{26} and chemioterapic agents.\textsuperscript{27} Considering the well documented medicinal utility of anthranilic acid and oxalamide derivatives, these tethered combinations of the two scaffolds afford new opportunities to probe their biological activity.

Based on above results and literature reports,\textsuperscript{3},\textsuperscript{4},\textsuperscript{6,}\textsuperscript{28} a plausible mechanism for the rearrangement was proposed. First, the process was believed to proceed through the classical Meinwald rearrangement (Scheme 1, path a) of 3-(2-nitrophenyl)oxirane-2-carboxamides with the cleavage of the C2–O bond in its initial stage (3 → A). The resulting ketone A bearing an active \(\alpha\)-methylene group undergoes a new rearrangement according to the mechanism of the known Baeyer–Drewson indigo synthesis\textsuperscript{28} with the formation of intermediate C, which is further subjected to acid-catalyzed ring opening (either C → D → E through pathway 1 or C → I → J → F through pathway 2).
involving hydration and dehydration processes (E → F → G → H → 4 through pathway 1 and F → G → H → 4 through pathway 2) with the participation of nitro-group and α-methylene functionalities. As a result, the reduction of the nitro-group and the transformation of the C3 atom of epoxide to the carbonyl functionalities occurs (Scheme 3).

The structures of 4a–h were established unambiguously by various 1D/2D NMR correlation methods. First, the proton spin systems of the Ar1 and Ar2 moieties were identified by COSY/TOCSY methods. After that, the structures of both halves up to carbonyl groups (C1 and C2) were established (boldfaced on Fig. 1) from the 1H–13C and 1H–15N HSQC/HMBC connectivities. Finally, both halves were linked into a single whole on the basis of the NOEs between protons of these two fragments:

Fig. 2 ORTEP plot of compounds 4a (a) and 4b (b) partial numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H-atoms are represented in stick mode for clarity.

![ORTEP plot](image.png)

Table 3 Synthesis of 2-(2-oxo-2-phenylacetamido)benzoic acids 7a–d

<table>
<thead>
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<th>R²</th>
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<td>1a</td>
<td>H</td>
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<td>4-MeOC₆H₄</td>
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<td>H</td>
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<td>5a</td>
<td>Cl</td>
<td>4-MeC₆H₄</td>
<td>6d</td>
<td>7d</td>
<td>89</td>
</tr>
</tbody>
</table>

a (Chloromethyl)arylketones 5a,b were obtained on a 0.1 mol scale at 10–20 °C by reaction of 1 equiv. chloroacetyl chloride with toluene (100 mL) and anisole (100 mL), respectively, with the use of 1.5 equiv. AlCl₃. b (Bromomethyl)arylketone 5e was obtained on a 0.1 mol scale at 30–55 °C by reaction of 1 equiv. 1-(3-nitrophényl)ethanone with 1 equiv. bromine in ethanol (100 mL). Yields refer to isolated products.

The next three methods include the direct amidation of isocyanates, α-keto benzotriazole and trichloropyruvamides with amines. The fifth method is a novel one and is based on green H₂O₂-promoted oxidative amidation of 2-oxoaldehydes with amines. Nevertheless, these methods have several drawbacks, such as harsh conditions, expensive reagents, poor atom-efficiency and limited substrate scope. Method proposed in this study demonstrated a new, efficient and metal-free synthesis of unsymmetrical oxalamides via novel rearrangement of easily available 3-(2-nitroaryl)-oxirane-2-carboxamides.

With this result in hand, we proceeded with the study of the scope of the rearrangement. As can be seen from the suggested mechanism of the rearrangement (Scheme 3) the transformation of 3-(2-nitroaryl)oxirane-2-carboxamides to the oxalamides involves the 3-(2-nitroaryl)oxirane fragment only. Thus, seeking to expand accessible skeletal diversity using the same reaction conditions, we anticipated that use of (3-(2-nitroaryl)oxiran-2-yl)(aryl)methanones 6a–d with the same necessary fragment would facilitate access to 2-(2-oxo-2-arylacetamido) benzoic acids (7a–d). Indeed the refluxing of oxiranes 6a–d in AcOH in the presence of catalytic amount of H₂SO₄ provides the desired mono-oxalamides 7a–d in good yields. Moreover, the reaction of 2-nitrobenzaldehyde (1a) and 5-chloro-2-
nitrobenzaldehyde (1b) with 2-chloro-1-(4-tolyl)ethanone (5a), 2-chloro-1-(4-methoxyphenyl)ethanone (5b) and 2-chloro-1-(3-nitrophenyl)ethanone (5c) under the Darzens condensation condition proceeded smoothly, and (3-(2-nitrophenyl)oxiran-2-yl)(aryl)methanones 6a–d were obtained in quantitative yields (Table 3). It should be pointed out that in this case, in contrast to the reactions of chloroaacetanilides 2,13 the process proceeds with high stereoselectivity with the formation of only trans-isomers of oxiranes 6a–d as the only products.

The structures of all compounds were proved by variety of 1D/2D NMR correlation methods (see ESI†).

Conclusion

In conclusion, we have discovered a new rearrangement of 3-(2-nitrophenyl)-oxirane-2-carboxamides proceeding in boiling AcOH in the presence of H2SO4. The rearrangement quantitatively produces the N-(2-carboxaryl)oxalamides as a result of cascade processes involving (a) the classical Meinwald rearrangement in its initial stage with the formation of ketone bearing an active α-methylene group, (b) transformation of carbonyl group of the ketone to the carboxylic functionality, (c) migration of active α-methylene group to the nitrogen atom of already reduced nitro group. The simple reaction conditions offer a potential for employing this method in the synthesis of complex molecules. It is anticipated that this methodology will have versatile applications in the practical syntheses of biologically important pharmaceutical molecules with anthranilic acid and oxalamide moieties. The methodology is applicable to synthesis of N-(2-carboxyphenyl)arylaxalmonooxamides from 3-(2-nitrophenyl)oxiran-2-yl)(aryl)methanones. Further extension of the reaction scope and the synthetic applications of this methodology are in progress at our laboratory.

Experimental section

General methods

All reagents and solvents were used as purchased, without further purification melting points were determined on a hot-stage apparatus. Infrared (IR) spectra samples in Nujol were recorded on a FT-IR spectrometer Bruker Vector-22 in the 400–4000 cm−1 range at optical resolution of 4 cm−1. The high resolution MALDI mass-spectra were obtained on UltraFlex III TOF/TOF instrument in positive reflectron mode; 2,5-DHB and p-NA were used as matrix and PEG-400 was used for calibration of accurate masses. All NMR experiments were performed with 600, 500 and 400 MHz (600 MHz for 1H NMR; 150.9, 125 and 100.6 MHz for 13C NMR; 60.8 and 50.7 MHz for 15N NMR) spectrometers equipped with 5 mm diameter gradient inverse broad band probehead and a pulsed gradient unit capable of producing magnetic field pulse gradients in the z-direction of 53.5 G cm−1. NMR experiments were carried out at 303 K. DPFGROE20 and TOCSY spectra were obtained using a Hermite-shaped pulse for selective excitation. Chemical shifts (δ in ppm) are referred to the solvent DMSO-d6 (δ = 2.49 ppm for 1H and 39.5 ppm for 13C NMR), to external CD3NO2 (380.2 ppm) for 15N NMR spectra (conversion factor to NH3: −380.2 ppm). 1H–1H coupling constants were computed according to Bally & Rablen’s recommendations.24 First the geometry was optimized at the B3LYP/6-31G(d) level. Then NMR single-point calculation of the Fermi contact J values was run at the B3LYP/6-31G(d,p) level. These values were scaled then by a factor of 0.9117. The quantum chemical calculations were performed using a Gaussian 03 software package.27

General procedure for the Darzens condensation. A solution of EtONa obtained when dissolving Na (0.73 g, 0.032 g-atom) in EtOH (20 mL) was added at room temperature to the stirred solution of 2-nitrobenzaldehyde (4.08 g, 0.027 mol) with the corresponding compound 2 (0.027 mol) in EtOH (70 mL). The stirring is continued for 7 h. Treatment of the reaction mixtures as is usual for previous cases13 led to the products 3.

trans-3-(2-Nitrophenyl)-N-phenyloxirane-2-carboxamides (3a).

<table>
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<th>Structure</th>
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<td>EtONa</td>
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<td>Other reagents</td>
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Tan powder (7.68 g, 0.027 mol, 87% yield): mp 180–181 °C; 1H NMR (600 MHz, DMSO-d6) δ 10.35 (s, 1H, NH), 8.20 (d, J = 8.2 Hz, 1H, H3-Ar1), 7.85 (dd, J = 7.6, 7.6 Hz, 1H, H5-Ar1), 7.65–7.69 (m, 3H, H2,2-Ar2; H4-Ar1), 7.59 (d, J = 7.9 Hz, 1H, H6-Ar1), 7.36 (dd, J = 7.9, 7.9 Hz, 2H, H5-Ar2), 7.12 (dd, J = 7.6, 7.2 Hz, 1H, H4-Ar2), 4.68 (d, J = 1.8 Hz, 1H, H3), 3.65 (d, J = 1.8 Hz, 1H, H2); 13C NMR (150.9 MHz, DMSO-d6) δ 164.6 (C1), 147.46 (C2-Ar1), 138.23 (C1-Ar2), 134.66 (C5-Ar1), 132.19 (C1-Ar1), 129.50 (C4-Ar1), 128.78 (C3-Ar2), 126.73 (C5-Ar1), 124.65 (C3-Ar1), 123.91 (C4-Ar2), 119.45 (C2-Ar2), 57.37 (C2), 55.14 (C3); 15N NMR (60.8 MHz, DMSO-d6) δ 371.6 (NO2), 131.2 (NH). IR (nujol): ν 3279, 1674, 1604, 1533, 1525 cm−1; HRMS (MALDI) calcd for C13H12N2O4 [M + Cs]⁺ 416.9846, found 416.9843; anal. calcd for C13H12N2O4: C, 63.83; H, 4.25; N, 9.85; found: C, 63.42; H, 4.13; N, 9.92.

trans-N-(4-Bromophenyl)-3-(2-nitrophenyl)oxirane-2-carboxamide (3b).

<table>
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Tan powder (8.33 g, 0.023 mol, 85% yield): mp 191–192 °C; 1H NMR (600 MHz, DMSO-d6) δ 10.50 (s, 1H, NH), 8.19 (dd, J = 8.2, 1.0 Hz, 1H, H3-Ar1), 7.85 (dd, J = 7.7, 7.2 Hz, 1H, H5-Ar1), 7.67 (dd, J = 8.2, 7.7, 1.0 Hz, 1H, H4-Ar1), 7.64 (d, J = 8.7 Hz, 2H, H2,4-Ar2), 7.58 (d, J = 7.7 Hz, 1H, H6-Ar1), 7.54 (d, J = 8.7 Hz, 2H, H3,5-Ar2), 4.68 (d, J = 1.8 Hz, 1H, H3), 3.64 (d, J = 1.8 Hz, 1H, H2); 13C NMR (100.6 MHz, DMSO-d6) δ 164.74 (C1), 147.45 (C2-Ar1), 137.59 (C1-Ar2), 134.69 (C5-Ar1), 132.09 (C4-Ar1), 131.64 (C4-Ar2), 129.56 (C4-Ar1), 126.73 (C5-Ar1), 124.68 (C3-Ar1), 121.43 (C2-Ar2), 115.61 (C4-Ar2), 57.36 (C2), 55.27 (C3); 15N NMR (60.8 MHz, DMSO-d6) δ 371.5 (NO2), 131.2 (NH). IR (nujol): ν 3362, 1691, 1591, 1521 cm−1; HRMS (MALDI) calcd for C13H11BrN2O4 [M + Cs]⁺ 494.8951; 496.8932, found 494.8946.
Tan powder (6.12 g, 0.021 mol, 76% yield): mp 140–143 °C; 1H NMR (600 MHz, DMSO-d6): δ 10.29 (s, 1H, NH); 8.21 (dd, J = 8.2, 1.1 Hz, 1H, H3-Ar1), 7.86 (ddd, J = 7.5, 7.2, 1.1 Hz, 1H, H5-Ar1), 7.68 (ddd, J = 7.9, 7.8, 1.4 Hz, 1H, H4-Ar1), 7.59 (d, J = 7.6 Hz, 1H, H2-Ar1), 7.51 (br.s, 1H, H2-Ar2), 7.45 (br.d, J = 8.2 Hz, 1H, H6-Ar2), 7.24 (dd, J = 7.8, 7.7 Hz, 1H, H5-Ar2), 6.94 (d, J = 7.4 Hz, 1H, H4-Ar2), 4.68 (d, J = 2.0 Hz, 1H, H3), 3.65 (d, J = 2.0 Hz, 1H, H2), 2.31 (s, 3H, CH3); 13C NMR (125.8 MHz, DMSO-d6) δ 164.39 (C1), 147.45 (C2-Ar1), 138.17 (C3-Ar2), 138.05 (C1-Ar2), 134.69 (C5-Ar1), 132.24 (C1-Ar1), 129.51 (C4-Ar1), 124.64 (C5-Ar2), 126.73 (C6-Ar1), 124.67 (C4-Ar2), 124.62 (C3-Ar1), 119.96 (C2-Ar2), 116.65 (C6-Ar2), 57.38 (C2), 55.14 (C3), 21.09 (Me); 15N NMR (60.8 MHz, DMSO-d6) δ 371.6 (NO2), 132.5 (NH); IR (nujol): ν 3252, 1667, 1611, 1556, 1524 cm⁻¹; HRMS (MALDI) caleq C16H14N2O5 [M + Cs⁺] 343.0003, found 343.9994; anal. caleq for C16H14N2O5: C, 64.42; H, 4.73; N, 9.39; found: C, 64.86; H, 4.72; N, 9.41.

trans-N-(4-Methoxyphenyl)-3-(2-nitrophenyl)oxirane-2-carboxamide (3d).

Brown powder (5.34 g, 0.017 mol, 62% yield): mp 168–169 °C; 1H NMR (600 MHz, DMSO-d6): δ 10.23 (s, 1H, NH); 8.21 (dd, J = 8.2, 1.1 Hz, 1H, H3-Ar1), 7.86 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H, H5-Ar1), 7.68 (ddd, J = 7.8, 7.8, 1.3 Hz, 1H, H4-Ar1), 7.49–7.60 (m, 3H, H2,4-Ar2; H6-Ar1), 6.93 (d, J = 9.1 Hz, 2H, H3,5-Ar2), 4.68 (d, J = 1.9 Hz, 1H, H3), 3.75 (s, 3H, OCH3), 3.61 (d, J = 1.9 Hz, 1H, H2); 13C NMR (150.9 MHz, DMSO-d6) δ 163.98 (C1), 155.67 (C4-Ar2), 147.47 (C2-Ar1), 134.69 (C5-Ar1), 132.28 (C1-Ar1), 131.40 (C2-Ar1), 129.51 (C4-Ar1), 126.75 (C6-Ar1), 124.68 (C3-Ar1), 121.10 (C2-Ar2), 113.94 (C3-Ar2), 57.44 (C2), 55.17 (Ome), 55.10 (C3); 15N NMR (60.8 MHz, DMSO-d6) δ 371.8 (NO2-Ar1), 130.6 (NH); IR (nujol): ν 3360, 1711, 1697, 1608, 1595, 1522 cm⁻¹; HRMS (MALDI) caleq for C18H16N2O5 [M + Cs⁺] 489.0057, found 489.0055; anal. caleq for C18H16N2O5: C, 60.67; H, 4.53; N, 7.86; Found: C, 60.48; H, 4.48; N, 7.93.

trans-3-(2-Nitro-5-chlorophenyl)-N-phenylxirane-2-carboxamide (3g).

White powder (5.25 g, 0.016 mol, 61% yield): mp 156–158 °C; 1H NMR (600 MHz, DMSO-d6): δ 10.38 (s, 1H, NH), 8.25 (d, J = 8.8 Hz, 1H, H3-Ar1), 7.75 (dd, J = 8.8, 2.4 Hz, 1H, H4-Ar1), 7.67 (d, J = 8.4 Hz, 2H, H2,6-Ar2), 7.56 (d, J = 2.4 Hz, 1H, H6-Ar1), 7.38 (dd, J = 8.4, 7.5 Hz, 2H, H3,5-Ar2), 7.13 (ddd, J = 7.5, 7.4, 1.0 Hz, 1H, H4-Ar2), 4.72 (d, J = 2.0 Hz, 1H, H2), 3.72 (d, J = 2.0 Hz, 1H,
Light brown powder (0.46 g, 1.62 mmol, 97% yield): mp 227–228 °C; 1H NMR (600 MHz, DMSO-d6) δ 8.18 (dd, J = 8.1, 1.0 Hz, 1H, H3-Ar1), 7.04 (dd, J = 8.1, 1.0 Hz, 1H, H5-Ar1), 7.00 (ddd, J = 8.1, 1.0 Hz, 1H, H6-Ar1), 6.90 (ddd, J = 8.1, 1.0 Hz, 1H, H2-Ar2), 6.71 (ddd, J = 8.1, 1.0 Hz, 1H, H4-Ar2); 13C NMR (125.8 MHz, DMSO-d6) δ 168.84 (CO2H), 158.29 (2C=O), 158.03 (1C=O), 139.16 (C1-Ar2), 137.41 (C1-Ar2), 134.19 (C4-Ar1), 131.43 (C6-Ar1), 128.65 (C3-Ar2), 124.72 (C4-Ar2), 123.92 (C5-Ar1), 120.60 (C2-Ar2), 119.53 (C3-Ar1), 117.39 (C1-Ar1); 15N NMR (60.8 MHz, DMSO-d6) δ 126.8 (N2), 121.7 (N1); IR ν (nujol): ν 3329, 3179, 1678, 1586, 1528 cm⁻¹; HRMS (MALDI) caledfor C16H14N2O4 [M + Ca]⁺ 340.9536; found 340.9536; anal. caledfor C16H14N2O4; C, 51.93; H, 3.87; N, 13.46. Found: C, 51.93; H, 3.87; N, 13.46.

General procedure for the rearrangement. Concd H2SO4 (0.1 mL) was added to the solution of 3 (1.67 mmol) in AcOH (5 mL). The reaction mixture was boiled for 3 h and then poured into water. The precipitate thus formed was collected by filtration, washed with water and dried.

N1-(2-Carboxyphenyl)-N2-(9-phenyloxalamide (4a).

Grey powder (0.61 g, 1.67 mmol, 100% yield): mp 281–283 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.72 (s, 1H, NH1), 11.04 (s, 1H, NH2), 8.68 (d, J = 8.2 Hz, 1H, H3-Ar1), 8.07 (dd, J = 8.2, 1.5 Hz, 1H, H6-Ar1), 7.85 (d, J = 8.7 Hz, 2H, H2,6-Ar2), 7.71 (dd, J = 7.9, 7.7, 1.5 Hz, 1H, H4-Ar1), 7.57 (d, J = 8.7 Hz, 2H, H3,5-Ar2), 7.28 (ddd, J = 7.7, 7.7, 1.0 Hz, 1H, H5-Ar1); 13C NMR (150.9 MHz, DMSO-d6) δ 168.82 (CO2H), 158.18 (2C=O), 158.03 (1C=O), 139.10 (C2-Ar1), 136.84 (C1-Ar2), 134.20 (C4-Ar1), 131.49 (C3-Ar2), 131.41 (C6-Ar1), 129.95 (C5-Ar1), 122.54 (C2-Ar2), 119.54 (C3-Ar1), 117.32 (C1-Ar1), 116.65 (C4-Ar2); 15N NMR (60.8 MHz, DMSO-d6) δ 126.6 (N2), 122.2 (N1); IR ν (nujol): ν 3301, 3189, 1687, 1584, 1519 cm⁻¹; HRMS (MALDI) caledfor C21H12BrN2O4 [M + Na]⁺ 384.9794; 386.9776, found 384.9795; 386.9786; anal. caledfor C21H12BrN2O4; C, 49.61; H, 3.05; Br, 22.00; N, 7.71. Found: C, 49.38; H, 3.02; Br, 22.07; N, 7.69.

N1-(2-Carboxyphenyl)-N2-(3-methylphenyloxalamide (4c).

Grey powder (0.46 g, 1.54 mmol, 92% yield): mp 203–205 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.72 (s, 1H, NH1), 10.79 (s, 1H, NH2), 8.70 (d, J = 8.4, 1.0 Hz, 1H, H3-Ar1), 8.08 (dd, J = 7.9, 1.6 Hz, 1H, H6-Ar1), 7.73 (br.s, 1H, H2-Ar2), 7.72 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H, H4-Ar1), 7.64 (br.d, J = 8.3 Hz, 1H, H6-Ar1), 7.29 (ddd, J = 7.9, 7.9, 1.2 Hz, 1H, H5-Ar1), 7.27 (dd, J = 7.8, 7.8 Hz, 1H, H5-Ar2), 7.00 (d, J = 7.6 Hz, 1H, H4-Ar2), 2.33 (s, 3H, CH3); 13C NMR (125.8 MHz, DMSO-d6) δ 168.83 (CO2H), 158.32 (2C=O), 157.95 (1C=O), 139.16 (C2-Ar1), 137.92 (C3-Ar2), 137.31 (C1-Ar2), 134.24 (C4-Ar1), 131.44 (C6-Ar1), 128.50 (C5-Ar2), 125.44 (C4-Ar2), 123.94 (C5-Ar1), 121.06 (C2-Ar2), 119.53 (C3-Ar1), 117.82 (C6-Ar2), 116.31 (C4-Ar1), 21.12 (Me); 15N NMR (50.7 MHz, DMSO-d6) δ 126.9 (N2), 121.8 (N1); IR ν (nujol): ν 3317, 3187, 1678, 1587, 1528 cm⁻¹; HRMS (MALDI) caledfor C16H14N2O4 [M + Ca]⁺ 431.0003, found 431.0004; anal. caledfor C16H14N2O4; C, 64.42; H, 4.73; N, 9.39. Found: C, 64.31; H, 4.68; N, 9.42.

N1-(2-Carboxyphenyl)-N2-(4-bromophenyloxalamide (4b).

Grey powder (0.50 g, 1.59 mmol, 95% yield): mp 272–273 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.70 (s, 1H, NH1), 10.78 (s, 1H, NH2), 8.69 (ddd, J = 8.4, 7.7, 1.0 Hz, 1H, H3-Ar1), 8.07 (dd, J = 8.2, 1.6 Hz, 1H, H6-Ar1), 7.78 (d, J = 9.1 Hz, 2H, H2,6-Ar2), 7.71...
Light green powder (0.53, 1.61 mmol, 96% yield): mp 254–256 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.90 (s, 1H, NH1), 11.40 (s, 1H, N2H), 8.90 (dd, J = 2.0, 2.0 Hz, 1H, H2-Ar2), 8.69 (d, J = 8.2 Hz, 1H, H3-Ar1), 8.27 (dd, J = 7.9, 1.2 Hz, 1H, H6-Ar2), 8.08 (dd, J = 7.9, 1.2 Hz, 1H, H6-Ar1), 8.02 (dd, J = 7.9, 1.8 Hz, 1H, H4-Ar2), 7.66–7.72 (m, 2H, H5-Ar2/H4-Ar1), 7.28 (dd, J = 7.8, 7.2 Hz, 1H, H5-Ar1); 13C NMR (150.9 MHz, DMSO-d6) δ 168.93 (CO2H), 158.76 (2C=O), 157.68 (1C=O), 147.87 (C3=Ar2), 139.05 (C2=Ar1), 138.71 (C1=Ar), 134.02 (C4=Ar1), 131.43 (C6=Ar1), 130.09 (C5=Ar2), 126.68 (C6=Ar2), 123.97 (C5=Ar1), 119.51 (C3=Ar2), 119.17 (C4=Ar2), 117.80 (C2=Ar2), 141.81 (C2=Ar2); 15N NMR (60.8 MHz, DMSO-d6) δ 370.1 (NO2), 126.6 (N2), 122.2 (N1); IR (nujol): ν 3326, 3188, 1690, 1589, 1532 cm⁻¹; HRMS (MALDI) calculated for C12H11N3O5 [M + Na]+ = 352.0540, found 352.0563; anal. calcld for C12H11N3O5: C, 54.72; H, 3.37; N, 12.76. Found: C, 54.82; H, 3.43; N, 12.68.

N1-(4-Chloro-2-carboxyphenyl)-N2-(3-nitrophenyl)oxalamide (4e).

Brown powder (0.34 g, 1.62 mmol, 97% yield): mp 267–268 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.51 (s, 1H, NH1), 8.65 (d, J = 8.2 Hz, 1H, H3-Ar1), 8.36 (br.s, 1H, NH2), 8.05 (br.s, 1H, NH2), 8.04 (dd, J = 8.0, 1.6 Hz, 1H, H6-Ar2), 7.68 (dd, J = 7.9, 7.5, 1.5 Hz, 1H, H4-Ar4), 7.25 (dd, J = 7.6, 7.6, 1.0 Hz, 1H, H5-Ar4); 13C NMR (125.8 MHz, DMSO-d6) δ 168.66 (CO2H), 161.57 (1C=O), 158.73 (2C=O), 139.19 (C2=Ar4), 134.13 (C4=Ar4), 131.38 (C5=Ar4), 123.70 (C3=Ar4), 119.47 (C2=Ar1), 117.22 (C1=Ar); 15N NMR (50.7 MHz, DMSO-d6) δ 103.5 (N2), 121.3 (N1); IR (nujol): ν 3538, 3465, 3321, 3168, 2719, 1683, 1592, 1537, 1272, 752 cm⁻¹; HRMS (MALDI) calculated for C12H11N3O5 [M + 2C = H⁻] = 472.8509, found 472.8491; anal. calcld for C12H11N3O5: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.90; H, 3.39; N, 13.42.

Synthesis of 3-(2-Nitroaryl)oxiran-2-yl(aryl)methanones (6a–d). Synthesis of 3-(2-nitroaryl)oxiran-2-yl(aryl)methanones (6a–d) was performed according to the general procedure for the Darzens condensation with the use of corresponding (halomethyl)arylateketones (5a–e) instead of chloroacetamides (2a–g).

In these cases as distinct from the synthesis of 3-(2-nitroaryl) oxiran-2-carboxamides (3a–h) the reactions are completed for 0.5 h. The products precipitated during the reaction and did not require any purification except washing with water (3 x 25 ml).

trans-3-(2-Nitrophenyl)oxiran-2-yl(4-toly)methanone (6a).

Violet powder (0.34 g, 1.62 mmol, 97% yield): mp 267–268 °C; 1H NMR (600 MHz, DMSO-d6) δ 12.51 (s, 1H, NH1), 8.65 (d, J = 8.2 Hz, 1H, H3-Ar1), 8.36 (br.s, 1H, NH2), 8.05 (br.s, 1H, NH2), 8.04 (dd, J = 8.0, 1.6 Hz, 1H, H6-Ar2), 7.68 (dd, J = 7.9, 7.5, 1.5 Hz, 1H, H4-Ar4), 7.25 (dd, J = 7.6, 7.6, 1.0 Hz, 1H, H5-Ar4); 13C NMR (125.8 MHz, DMSO-d6) δ 168.66 (CO2H), 161.57 (1C=O), 158.73 (2C=O), 139.19 (C2=Ar4), 134.13 (C4=Ar4), 131.38 (C5=Ar4), 123.70 (C3=Ar4), 119.47 (C2=Ar1), 117.22 (C1=Ar); 15N NMR (50.7 MHz, DMSO-d6) δ 103.5 (N2), 121.3 (N1); IR (nujol): ν 3538, 3465, 3321, 3168, 2719, 1683, 1592, 1537, 1272, 752 cm⁻¹; HRMS (MALDI) calculated for C12H11N3O5 [M + 2C = H⁻] = 472.8509, found 472.8491; anal. calcld for C12H11N3O5: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.90; H, 3.39; N, 13.42.
Ar1), 8.0 (d, J = 8.2 Hz, 2H, H3,5-Ar2), 7.88 (ddd, J = 7.6, 7.5, 0.8 Hz, 1H, H5-Ar1), 7.65–7.71 (m, 2H, H4,6-Ar1), 7.37 (d, J = 8.2 Hz, 2H, H2,6-Ar1), 4.74 (d, J = 2.1 Hz, 1H, H2), 4.56 (d, J = 2.1 Hz, 1H, H3), 2.41 (s, 3H, Me); 13C NMR (100 MHz, DMSO-d6) δ 192.14 (1C, C=O), 147.47 (C2-Ar1), 144.72 (C4-Ar2), 134.60 (C5-Ar1), 132.70 (C1-Ar1), 129.47 (C4-Ar1), 129.38 (C2-Ar2), 128.50 (C3-Ar2), 127.02 (C6-Ar1), 124.62 (C3-Ar1), 58.34 (C2), 57.15 (C3), 21.19 (Me). IR (nujol): v 1682, 1522 cm⁻¹.

HRMS (MALDI) calcd for C16H13NO4 [M + Cs]+ 415.9894, found 415.9887; anal. calcd for C16H13NO4: C, 64.39; H, 4.51; N, 4.77.

Synthesis of 2-(2-oxo-2-arylacetamido)benzoic acids (7a–d). Synthesis of 2-(2-oxo-2-arylacetamido)benzoic acids (7a–d) was performed according to the general procedure for the rearrangement with the use of corresponding 3-(2-nitroxyloxiran-2-yl)arylcarboxamides (6a–d) instead of 3-(2-nitroxyloxiran-2-carboxamides (2a–h)). Products 7a,b were purified by washing with acetone (3 × 1 mL), products 7c,d - by recrystallization from AcOH.

2-[2-Oxo-2-(4-tolyl)acetamido]benzoic acid (7a).

Brown powder (0.35 g, 1.25 mmol, 75% yield): mp 199–201 °C; 1H NMR (400 MHz, DMSO-d6) δ 12.72 (s, 1H, NH), 8.64 (d, J = 7.5 Hz, 1H, H3-Ar1), 8.14 (d, J = 7.8 Hz, 2H, H2,6-Ar2), 8.04 (dd, J = 8.1, 1.0 Hz, 1H, H6-Ar1), 7.71 (dd, J = 7.6, 7.5 Hz, 1H, H4-Ar1), 7.37 (d, J = 7.8 Hz, 2H, H3,5-Ar2), 7.28 (dd, J = 7.5, 7.9 Hz, 1H, H5-Ar1), 2.42 (s, 3H, Me); 13C NMR (125.8 MHz, DMSO-d6) δ 187.00 (2C, C=O), 169.15 (CO2H), 160.57 (1C, C=O), 145.42 (C4-Ar2), 139.28 (C2-Ar2), 134.19 (C4-Ar1), 131.41 (C6-Ar1), 130.94 (C2-Ar2), 130.38 (C1-Ar2), 129.27 (C3-Ar1), 124.00 (C5-Ar1), 21.39 (Me). IR (nujol): v 3363, 1678, 1604, 1586, 1521, 1262 cm⁻¹; HRMS (MALDI) calcd for C16H13NO4 [M + Cs]+ 415.9894, found 415.9887; anal. calcd for C16H13NO4: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.92; H, 4.68; N, 4.71.
Ar1), 125.61 (C4-Ar2), 123.88 (C5-Ar1), 120.04 (C3-Ar1), 117.60 (C1-Ar1), 114.10 (C3-Ar2), 55.70 (OMe). IR (nujol): v 3472, 3258, 1702, 1674, 1601, 1584, 1528, 1260 cm⁻¹; HRMS ([M + Cs]⁺) calcd for C₁₆H₁₂ClNO₄ [M + 2Cs⁺] 578.8545, found 578.8545; anal. calcd for C₁₆H₁₂ClNO₄: C, 50.59; H, 3.27; N, 7.56.

References


Conflict of interest

The authors declare no competing financial interest.

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