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UFU ('Ullmann–Finkelstein–Ullmann'): a new multicomponent reaction

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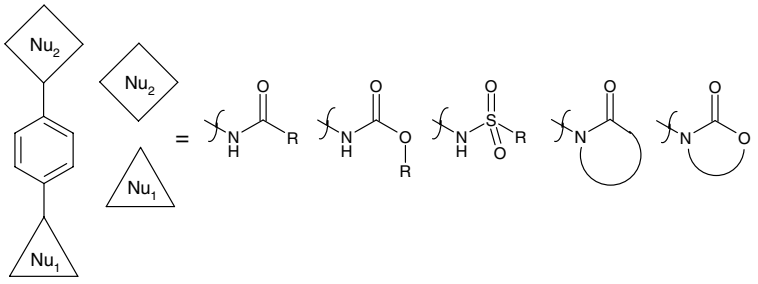
Abstract—We developed conditions to carry out the first 'one-pot' Ullmann–Finkelstein–Ullmann multicomponent reaction reported. This reaction allows the one-pot synthesis of dissymmetrical para-disubstituted benzene scaffold from 1-bromo-4-iodobenzene and two N-nucleophiles. CuI/*N*,*N*′-dimethyl-cyclohexane-1,2-diamine was used as a catalyst/ligand couple, K_3PO_4 as a base and the reaction was performed in dioxane.

1. Introduction

Nonsymmetrical para-disubstituted benzene is a common scaffold found in many biologically active compounds. In particular, acylated or sulphonylated paraphenylenediamine presented in Scheme 1 are well-represented in bioactive compounds databases.

Antiviral,[1] anticoagulant,[2] antisclerosis[3] or antineoplastic[4] activities have been reported for these structures. Some of them have even entered clinical development such as Tomeglovir an antiviral, or Rivaroxaban, (BAY 59-7939) which prevents thrombin generation in the coagulation pathway[2] (Scheme 2).

These biological data led us to design a simple synthesis of dissymmetrical acylated or sulfonylated para phenylenediamines, different from reported synthetic routes that usually involve acylations. We thus developed a copper-catalysed Ullmann–Finkelstein–Ullmann multicomponent reaction. The copper-catalysed couplings have been widely studied by Buchwald.[5] The 'Ullmann[6]' N-arylation[5] of amides and the 'Finkelstein' [7] I–Br exchange[8] have been improved using catalytic amount of



Scheme 1. General structure of para-disubstituted benzene scaffold.

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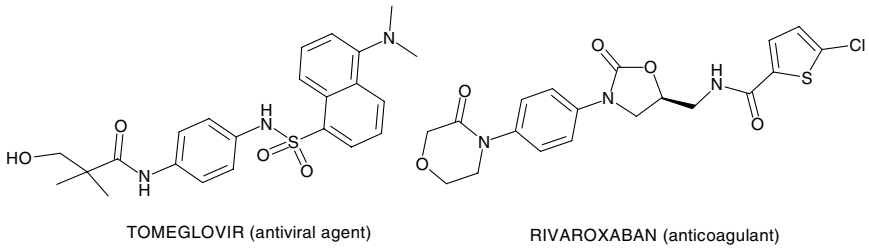


Scheme 2. Tomeglovir and Rivaroxaban.

CuI and an appropriate ligand. In order to introduce diversity on a simple benzene scaffold, we designed an extension of our UF tandem reaction[9] by exploring the possibility to perform a second Ullmann step in a 'one-pot' manner. Our aim was to determine the best conditions and types of nucleophiles for the synthesis of dissymmetrical products. We postulated that the reaction with one of the nucleophiles had to be faster than the other to allow a sequential course of the reactions and yield quantitatively the dissymmetrical compound. (Scheme 3).

In a first approach we determined the reaction rate of six nucleophiles (two carbamates **1** and **4**, three amides **3**, **5** and **6** and one sulfonamide **2**) in a typical Ullmann N-arylation. Each nucleophile was reacted with Iodobenzene, a catalytic amount of CuI and *N*,*N*′-dimethyl-cyclohexane-1,2-diamine, and K_3PO_4 as a base in dioxane following the conditions described by Buchwald.[5] The disappearance of iodobenzene was monitored by HPLC using a calibration curve based on UV absorbance, using 1,2,4,5-tetramethylbenzene as an internal standard. Based on these data (Fig. 1), we could identify pairs of nucleophiles displaying large differences in reactivity and postulated that they were the best candidates for a dissymmetrical UFU reaction.

In the case of oxazolidin-2-one **1** and *N*-methylbenzene-sulphonamide **2**,[10] iodobenzene is more than 70% converted after 15 min of reaction. Both reagents can be considered as fast nucleophiles. The fastest reagent **1** has been engaged in a UFU reaction in the presence of reagents **3** to **6** and sulfonamide **2**, an other fast-reacting nucleophile, was engaged with **4**, **5** and **6**. Though nucleophile **3** is less reactive (about 50% conversion after 15 min), we mixed it with the slowest reagents **5** and **6** to determine the limits of the rate difference in a pair of nucleophiles. Results are reported in Table 1. As we expected, good selectivity was obtained with pairs including nucleophiles **1** or **2** as fast nucleophiles. Six dissymmetrical products were obtained in high proportion and isolated with good yields. Only nucleophile **3** was not sufficiently reactive to allow a good selectivity.

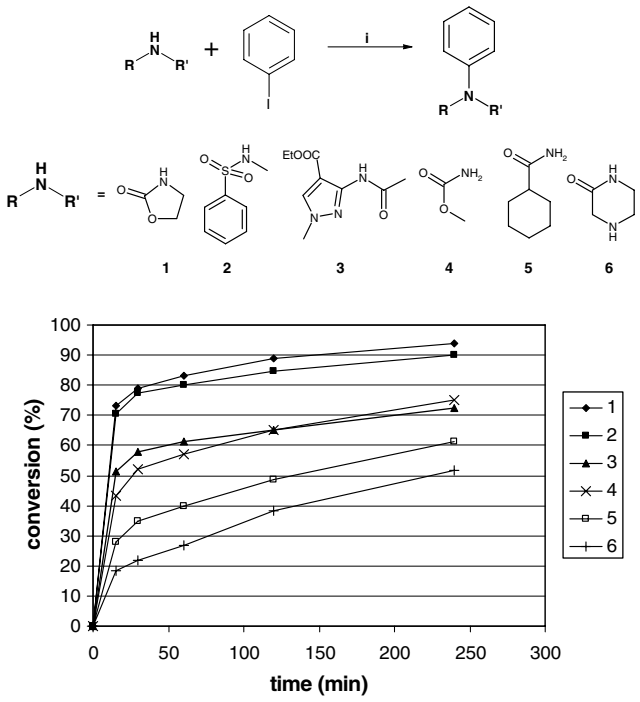
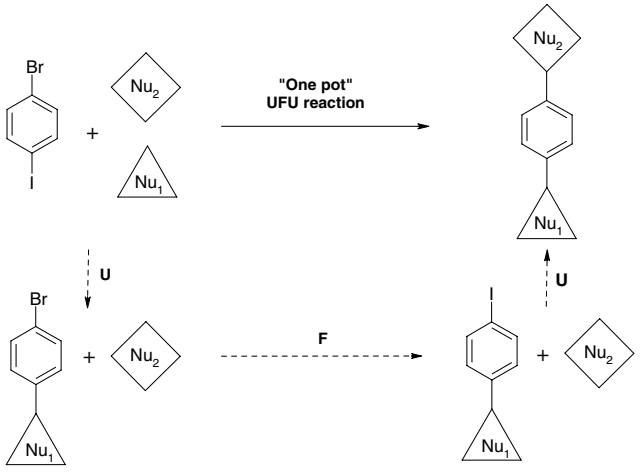


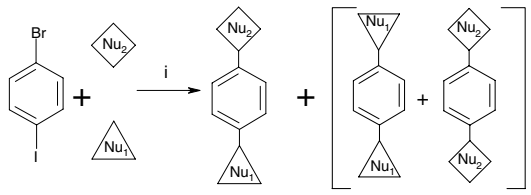
Figure 1. Iodobenzene conversion by nucleophiles **1** to **6**. Reagents and conditions: (i) 1 equiv of nucleophile, 1 equiv of iodobenzene, 0.1 equiv of CuI, 2 equiv of K_3PO_4, 0.2 equiv of *N*,*N*′-dimethyl-cyclohexane-1,2-diamine, 0.5 equiv of 1,2,4,5-tetramethylbenzene (durene), dioxane (0.5 M), 110 °C. Sampling performed under an argon overpressure. Ratio determined by UV detection at 215 nm.



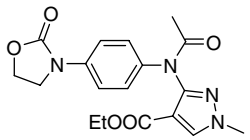
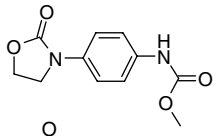
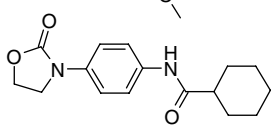
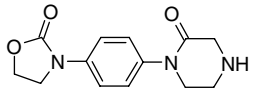
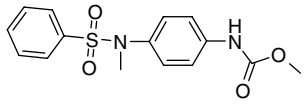
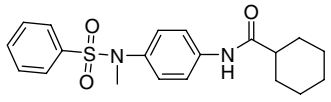
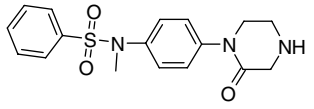
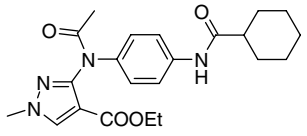
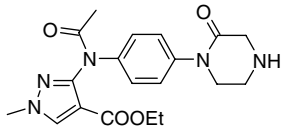
Scheme 3. Sequential course of the UFU 'one-pot' reaction **U**: Ullmann reaction, **F**: Finkelstein reaction Nu_1, Nu_2 = amide, sulphonamide, carbamate.

As presented in the introduction, we hypothesised that the UFU reaction proceeds in three successive steps:

Table 1. UFU reactions between Nu_1 (**1**, **2** and **3**) and Nu_2 (**3** to **6**)



[Nu_1,Nu_2] [Nu_1,Nu_1] [Nu_2,Nu_2]

Compound [Nu_1, Nu_2]	Structure	Ratio[a] (%)	Yield[b] (%)
[**1**,**3**]		80	53
[**1**,**4**]		82	60
[**1**,**5**]		85	64
[**1**,**6**]		95	70
[**2**,**4**]		92	83
[**2**,**5**]		92	70
[**2**,**6**]		96	81
[**3**,**5**]		57	ND
[**3**,**6**]		65	ND

Reagents and conditions: (i) 1 equiv of each nucleophile, 1 equiv of 1-bromo-4-iodobenzene, 0.2 equiv of CuI, 4 equiv of K_3PO_4, 0.4 equiv of *N*,*N*′-dimethyl-cyclohexane-1,2-diamine, dioxane (0.25 M), 110 °C, 22 h.

[a] Ratio = $[Nu_1,Nu_2]\times 100/([Nu_1, Nu_2]+[Nu_1, Nu_1]+[Nu_2,Nu_2])$ determined by UV detection at 215 nm.

[b] Isolated yield.

(1) Ullmann reaction with the most reactive nucleophile, (2) Finkelstein halogen exchange and (3) Ullmann reaction with the slowest nucleophile to yield the desired dissymmetrical compound. To confirm that assumption we performed a kinetic study with nucleophiles **1** and **6**. We monitored the formation of halogenated intermediates [**1**,**Br**] and [**1**,**I**]; the dissymmetrical compound [**1**,**6**]; and also the undesired symmetrical compounds [**1**,**1**] and [**6**,**6**] (Table 2).

After 30 min, reagent **1** was totally converted to the N-arylated derivatives [**1**,**X**]. [**1**,**Br**] was converted to [**1**,**I**]. After 18 h, the dissymmetrical product [**1**,**6**] was almost quantitatively formed. Base on this observation and the catalytic cycles already demonstrated for Ullmann and Finkelsein copper-catalysed reactions, we postulated a mechanism for the UFU reaction, using the succession of three catalytic cycles $\mathbf{U}_1$, **F** and $\mathbf{U}_2$ (Scheme 4).

2. Discussion

Through this work, we have identified two families of N-nucleophiles: cyclic carbamates and alkylated sulfonamides that can be used to perform UFU reaction in the presence of slow-reacting nucleophiles (lactams, amides and noncyclic carbamates) with a good dissymmetrical selectivity. According to the kinetic study of the Ullmann N-arylation for **1** ($pK_a = 20.8$ in DMSO[11]), **3** ($pK_a < 21$ in DMSO[12]) and **4** ($pK_a = 24.2$ in DMSO[11]), we observe that the arylation rate is (a) the highest with the most acidic nucleophiles and (b) lower for sterically hindered reagents. Both criteria (acidity and steric hindrance) shall guide the choice of the candidate pairs of reagents for a selective UFU reaction.

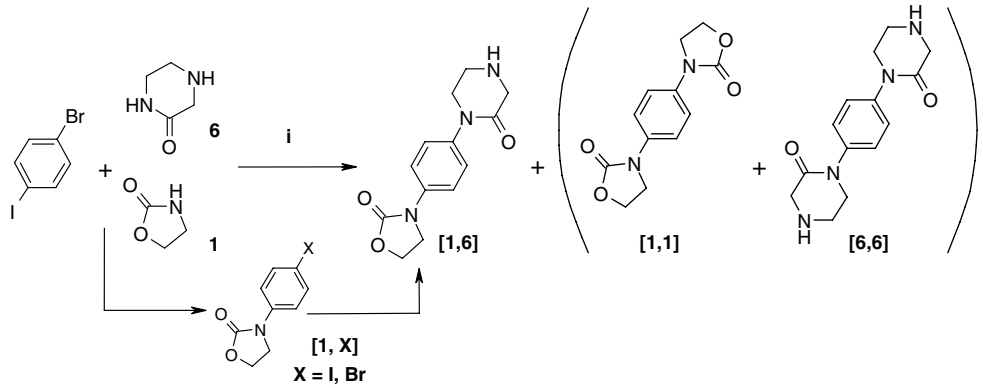
In order to extend the scope of our reaction, we mixed the nonalkylated benzenesulphonamide **7** with amide **5** using our UFU conditions (Scheme 5). Being less hindered than **1**, reagent **7** was thought to react even faster and give quantitatively the desired compound when mixed with the slow reagent **5**. Unexpectedly, the major product observed after 48 h was intermediate [**7**,**Br**], while only a trace of the expected product [**7**,**5**] could be detected.

We supposed that the N-arylsulphonamide [**7**,**Br**] intermediate could quench all further catalytic cycles. Indeed with a pK_a 2 units lower[13] than its unarylated homologue, the resulting conjugated base formed in higher proportion could trap most of the catalyst as $\mathbf{CuL_2Nu}$ copper complex and inhibit the multicomponent reaction. Moreover the high selectivity observed for the methylated analogue **2** in UFU reaction (Table 1) confirmed the key role played by the acidic NH of the sulfonamide [**7**,**Br**] in the inhibition phenomena.

3. Conclusion

This new UFU multicomponent reaction is a useful tool for the synthesis of paraphenylenediamine derivatives. It can be used to prepare large libraries for biomolecular screening. We describe three structural features that

Table 2. Conversion rate study of the UFU reaction with nucleophiles **1** and **6**



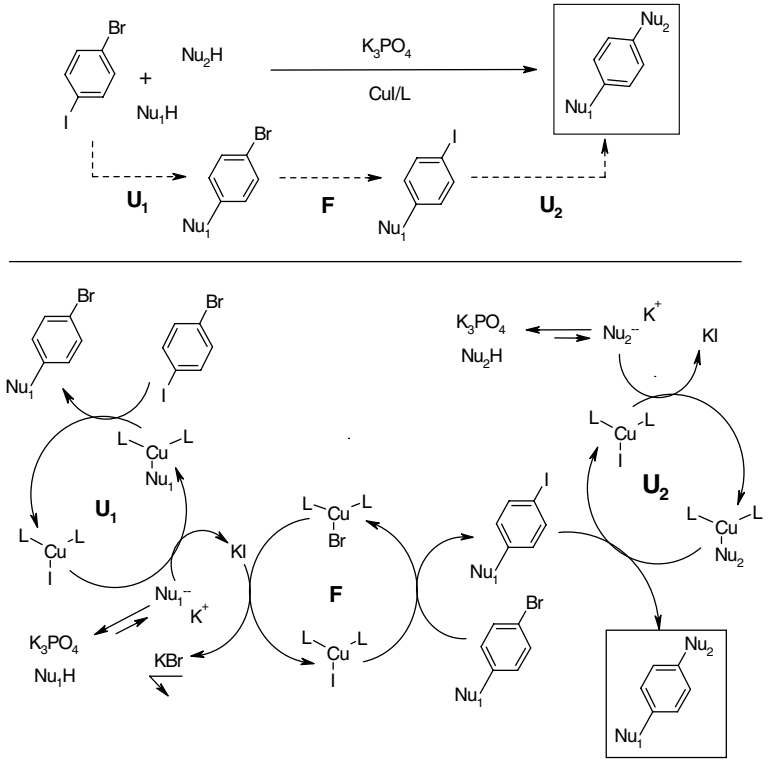
Time	Conversion of 1[a] (%)	[1,Br][a] (%)	[1,I][a] (%)	[1,6][a]	[1,1] + [6,6][a]
15 min	80	92	8	—	—
30 min	100	84	16	—	—
45 min	100	73	27	Trace[b]	—
60 min	100	66	34	Trace	—
2 h	100	54	46	Trace	—
3 h	100	36	46	18%	Trace
18 h	100	—	—	95%[c]	5%[c]

Reagents and conditions: (i) 1 equiv of **1** and **6**, 1 equiv of 1-bromo-4-iodobenzene, 0.2 equiv of CuI, 4 equiv of K_3PO_4, 0.4 equiv of N,N′-dimethylcyclohexane-1,2-diamine, dioxane (0.25 M), 110 °C.

[a] UV detection at 215 nm. Sampling performed under an argon overpressure.

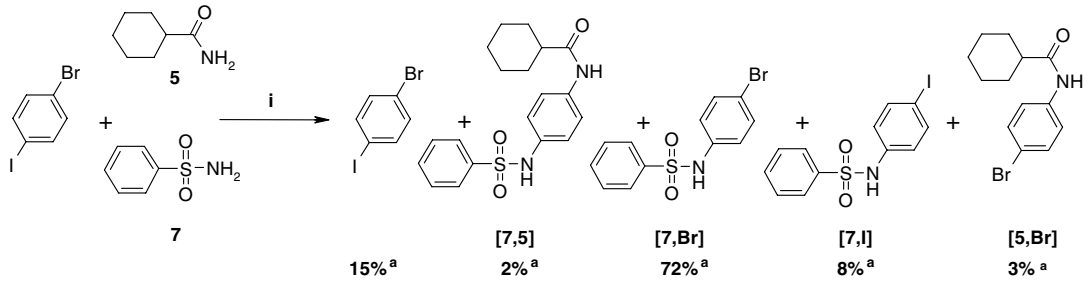
[b] Trace means detectable on MS spectrogram but irrelevant by UV detection.

[c] Relative ratio between dissymmetrical and symmetrical compounds.



Scheme 4. Supposed mechanism of the UFU reaction.

should be used to select reagent pairs and synthetic schemes. (1) Acidity, (2) steric hindrance and (3) potential ligand property of the arylated form of the fastest nucleophile.



Scheme 5. UFU reaction between **6** and **7**. Reagents and conditions: (i) 1 equiv of **6** and **7**, 1 equiv of 1-bromo-4-iodobenzene, 0.2 equiv of CuI, 4 equiv of K_3PO_4, 0.4 equiv of *N*,*N*′-dimethyl-cyclohexane-1,2-diamine, dioxane (0.25 M), 110 °C, 48 h. [a]UV detection at 215 nm.

4. Experimental

4.1. General procedure for Ullmann kinetic study

A dried Schlenck tube evacuated and backfilled with argon (×2) was charged with CuI (10 mg, 0.05 mmol), K_3PO_4 (213 mg, 1 mmol), the amide (0.5 mmol) and 1,2,4,5-tetramethylbenzene (33.5 mg, 0.25 mmol) under argon overpressure. Then dioxane (1 ml), the *N*,*N*′-dimethyl-cyclohexane-1,2-diamine (16 μl, 0.1 mmol) and iodobenzene (56 μl, 0.5 mmol) were injected in the tube. The sealed tube was stirred at 110 °C. Samplings were performed under argon overpressure at 15, 30, 60, 120, 240 min, diluted in MeOH 400 μl and filtered for LCMS analysis.

4.2. General procedure for Ullmann/Finkelsteïn/Ullmann reaction

A dried Schlenck tube evacuated and backfilled with argon (×2) was charged with CuI (20 mg, 0.1 mmol), K_3PO_4 (426 mg, 2 mmol), the 1-bromo-4-iodobenzene (145 mg, 0.5 mmol), and the two amides (0.5 mmol) under argon overpressure. Then the dioxane (2 ml) and the *N*,*N*′-dimethyl-cyclohexane-1,2-diamine (32 μl, 0.2 mmol) were injected in the tube. The sealed tube was stirred at 110 °C for 22 h. A solution of ammonia (28%, 2 ml) and water (25 ml) was sequentially added at rt to the reaction mixture. The resulting aqueous layer was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were dried on $MgSO_4$, filtered and evaporated under reduced pressure. The residue was triturated in an appropriate solvent or purified on silica gel.

4.3. 3-{Acetyl-[4-(2-oxo-oxazolidin-3-yl)-phenyl]-amino}-1-methyl-1*H*-pyrazole-4-carboxylic acid ethyl ester [1,3]

Work-up: The residue was purified on silica gel (cyclohexane/AcOEt: 5/5) to give a yellowish solid (99 mg).

Yield: 53%, mp: 162–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (s, 1H, C$H_{pyrazole}$); 7.50 (m, 4H, CH_{arom}); 4.48 (t, 2H, $J_{HH} = 7.5$ Hz, N–CH_2–CH_2–O); 4.29 (q, 2H, $J_{HH} = 7.1$ Hz, CH_3–CH_2–O); 4.06 (t, 2H, $J_{HH} = 7.5$ Hz, N–CH_2–CH_2–O); 3.89 (s, 3H, N–CH_3); 2.07 (s, 3H, CH_3–C=O); 1.34 (t, 3H, $J_{HH} = 7.1$ Hz, CH_3–CH_2–O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 135.4$ (*C*H$_{pyrazole}$); 128.9 (2 × *C*H$_{arom}$); 118.9 (2 × *C*H$_{arom}$); 61.9 (N–CH_2–*C*H_2–O); 60.6 (CH_3–*C*H_2–O); 45.2 (N–*C*H_2–CH_2–O); 40.0 (N–*C*H_3); 22.8 (*C*H_3–C=O); 14.3 (*C*H_3–CH_2–O); LCMS (EI): $m/z = 373$ (base peak).

4.4. [4-(2-Oxo-oxazolidin-3-yl)-phenyl]-carbamic acid methyl ester [1,4]

Work-up: the residue was triturated in CH_2Cl_2 (1.5 ml), the solid was then filtered and washed with CH_2Cl_2 (1.5 ml) to give a beige solid (71 mg).

Yield: 60%, mp: 218–223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.45$ (s, 4 H, CH_{arom}); 4.41 (t, 2H, $J_{HH} = 5$ Hz, N–CH_2–CH_2–O); 4.01 (t, 2H, $J_{HH} = 5$ Hz, N–CH_2–CH_2–O); 3.65 (s, 3H, O–CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 155.4$ (*C*=O); 154.5 (*C*=O); 135.4 (*C*q$_{arom}$); 133.7 (*C*q$_{arom}$) 119.1 (2 × *C*H$_{arom}$); 119.0 (2 × *C*H$_{arom}$); 61.9 (N–CH_2–*C*H_2–O); 52.1 (O–*C*H_3); 45.4 (N–*C*H_2–CH_2–O), LCMS (EI): $m/z = 237$ (base peak).

4.5. Cyclohexanecarboxylic acid [4-(2-oxo-oxazolidin-3-yl)-phenyl]-amide [1,5]

Work-up: The residue was purified on silica gel (cyclohexane/AcOEt: 6/4) to give a pale yellow solid (93 mg).

Yield: 64%, mp: 190–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.81$ (s, 1H, *H*N–C=O); 7.60 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 7.46 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 4.41 (t, 2H, $J_{HH} = 5$ Hz, N–CH_2–CH_2–O); 4.02 (t, 2H, $J_{HH} = 5$ Hz, N–CH_2–CH_2–O); 2.30 (Tt, 1H, $J_{HH} = 11.1$ Hz $J_{HH} = 3.6$ Hz, C$H_{cyclohexyl}$); 1.73 (m, 5H, C$H_{cyclohexyl}$); 1.30 (m, 5H, C$H_{cyclohexyl}$) ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 176.6$ (*C*=O); 155.4 (*C*=O); 135.8 (*C*q$_{arom}$); 134.0 (*C*q$_{arom}$); 119.9 (2 × *C*H$_{arom}$); 118.9 (2 × *C*H$_{arom}$); 61.9 (N–CH_2–*C*H_2–O); 45.4 (N–*C*H_2–CH_2–O); 45.3 (*C*H$_{cyclohexyl}$); 29.6 (2 × *C*H$_{2cyclohexyl}$); 25.9 (*C*H$_{2cyclohexyl}$); 25.7 (2 × *C*H$_{2cyclohexyl}$), LCMS (EI): $m/z = 287$ (base peak).

4.6. 1-[4-(2-Oxo-oxazolidin-3-yl)-phenyl]-piperazin-2-one [1,6]

Work-up: the aqueous phase (27 ml, ammonia + H_2O) was washed with AcOEt (2 × 5 ml) and then extracted with CH_2Cl_2 (3 × 25 ml). The CH_2Cl_2 fractions

were gathered, dried on $MgSO_4$, filtered and evaporated under reduced pressure to give a greenish solid (92 mg).

Yield: 70%; mp: 170–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.56$ (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 7.32 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 4.44 (t, 2H, $J_{HH} = 5$ Hz, N–CH$_2$–CH_2–O); 4.06 (t, 2H, $J_{HH} = 5$ Hz, N–CH_2–CH$_2$–O); 3.57 (t, 2H, $J_{HH} = 5.1$ Hz, N–CH_2–CH$_2$–N–C=O); 3.33 (s, 2H, N–CH_2–C=O); 3.01 (t, 2H, $J_{HH} = 5.1$ Hz, N–CH$_2$–CH_2–N–C=O) ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 126.8$ (2 × CH_{arom}); 118.9 (2 × CH_{arom}); 61.9 (N–CH$_2$–*C*H$_2$–O); 51.5 (N–*C*H$_2$–CH$_2$–N–C=O); 51.0 (N–CH$_2$–*C*=O); 45.4 (N–*C*H$_2$–CH$_2$–O); 44.9 (N–CH$_2$–*C*H$_2$–N–C=O), LCMS (EI): $m/z = 262$ (base peak).

4.7. [4-(Benzenesulfonyl-methyl-amino)-phenyl]-carbamic acid methyl ester [2,4]

Work-up: The residue was purified on silica gel (CH_2Cl_2/MeOH: 98/2) to give a colourless oil (133 mg).

Yield: 83%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (m, 3H, CH_{arom}); 7.47 (m, 2H, CH_{arom}) 7.33 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 7.01 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 3.77 (s, 3H, O–CH_3); 3.16 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.9$ (*C*=O); 137.2 (*C*q); 136.5 (*C*q); 136.3 (*C*q); 132.8 (*C*H$_{arom}$); 128.8 (*C*H$_{arom}$); 127.9 (*C*H$_{arom}$); 127.5 (*C*H$_{arom}$); 118.7 (*C*H$_{arom}$); 52.5 (O–*C*H$_3$); 38.3 (N–*C*H$_3$); LCMS (EI): $m/z = 321$ (base peak).

4.8. Cyclohexanecarboxylic acid [4-(benzenesulfonyl-methyl-amino)-phenyl]-amide [2,5]

Work-up: The residue was purified on silica gel (CH_2Cl_2/MeOH: 98/2) to give a white solid (131 mg).

Yield: 70%; mp: 218–223 °C; H NMR (300 MHz, $CDCl_3$): $\delta = 7.52$ (m, 7H, CH_{arom}); 7.01 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 3.15 (s, 3H, N–CH_3); 2.26 (Tt, 1H, $J_{HH} = 11.1$ Hz $J_{HH} = 3.6$ Hz, C$H_{cyclohexyl}$); 1.87 (m, 4H, C$H_{cyclohexyl}$); 1.70 (m, 1H, C$H_{cyclohexyl}$); 1.53 (Qd, 2H, $J_{HH} = 12$ Hz $J_{HH} = 2.7$ Hz, C$H_{cyclohexyl}$); 1.27 (m, 3H, C$H_{cyclohexyl}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.8$ (*C*=O); 137.5 (*C*q); 136.8 (*C*q); 136.2 (*C*q); 132.9 (*C*H$_{arom}$); 128.9 (*C*H$_{arom}$); 127.8 (*C*H$_{arom}$); 127.3 (*C*H$_{arom}$); 119.9 (*C*H$_{arom}$); 46.4 (*C*H$_{cyclohexyl}$); 38.3 (N–*C*H$_3$); 29.6 (2 × *C*H$_{2cyclohexyl}$); 25.6 (3 × *C*H$_{2cyclohexyl}$); LCMS (EI): $m/z = 373$ (base peak).

4.9. *N*-Methyl-*N*-[4-(2-oxo-piperazin-1-yl)-phenyl]-benzenesulfonamide [2,6]

Work-up: The residue was purified on silica gel (CH_2Cl_2/MeOH: 9/1) to give a yellow oil (140 mg).

Yield: 81%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (m, 3H, CH_{arom}); 7.47 (m, 3H, CH_{arom}); 7.27 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 7.12 (d, 2H, $J_{HH} = 9$ Hz, CH_{arom}); 3.73 (m, 4H, N–CH_2–CH$_2$–N–C=O + N–CH_2–C=O); 3.27 (t, 2H, $J_{HH} = 5.1$ Hz, N–CH$_2$–CH_2–N–C=O); 3.15 (s, 3H, N–CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.7$ (*C*=O); 141.1 (*C*q); 139.7 (*C*q); 136.4 (*C*q); 132.9 (*C*H$_{arom}$); 128.9 (*C*H$_{arom}$); 127.8 (*C*H$_{arom}$); 127.4 (*C*H$_{arom}$); 126.2 (*C*H$_{arom}$); 51.3 + 50.8 (N–*C*H$_2$–CH$_2$–N–C=O + N–*C*H$_2$–C=O); 43.4 (N–CH$_2$–*C*H$_2$–N–C=O); 38.1 (N–*C*H$_3$); LCMS (EI): $m/z = 346$ (base peak).

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