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Synthesis of 1- and 4-substituted piperazin-2-ones *via* Jocic-type reactions with *N*-substituted diamines

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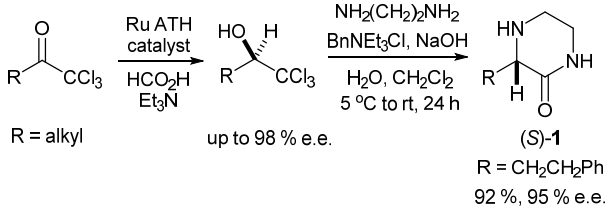
Enantiomerically-enriched trichloromethyl-containing alcohols, obtained by asymmetric reduction, can be transformed regioselectively into 1-substituted piperazinones by modified Jocic reactions with little or no loss of stereochemical integrity. This methodology can be easily used to synthesise important pharmaceutical compounds such as the fluorobenzyl intermediate of a known PGGTase-I inhibitor.

Introduction

Substituted piperazin-2-ones, and related piperazines, are important pharmacophores[1] which can be found in several medicinally relevant compounds, such as nonsteroidal androgen receptor antagonists,[2] hepatitis C virus replication inhibitors,[3] DPP-4 inhibitors,[4] elastase inhibitors,[5] PGGTase-I inhibitors,[6] antidepressants,[4b, 7] HDAC inhibitors,[8] neurokinin receptor antagonist GW597599,[9] melanocortin receptors,[4b, 8b, 10] CCR5 receptor antagonists,[11] anti-bacterials,[12] bradykinin receptor antagonists,[13] serotonin receptor antagonists,[14] GPIIb/IIIa antagonists,[15] PET probes for Rho-kinases,[16] and conformationally constrained peptides.[17] Whilst the synthesis of enantiomerically enriched 1- and 4-substitued piperazin-2-ones have been reported in the literature it still remains a great challenge.[1d, 5, 9, 18] To date enantiomerically-pure substituted piperazin-2-ones can be made by the dynamic resolution of α-halo chiral esters,[1d, 19] the kinetic resolution of *N*-heterocycles,[20] and manipulation of 'chiral pool' compounds such as naturally-occurring amino acids.[1a, 5, 17g, 18a]

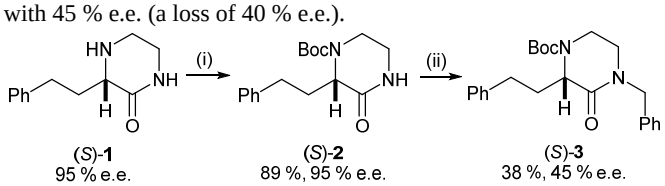
α-Trichloromethylalcohols are important intermediates in synthesis.[21] Previously, we reported the enantioselective reduction of trichloromethyl ketones using ruthenium transfer hydrogenation catalysts[22] and the subsequent Jocic-type reactions[23] of the products to give enantiomerically enriched amino-amides.[24]



Scheme 1 Previously reported work.

Results

Due to the medicinal relevance of 1-substituted piperazin-2-ones[25] we attempted to develop a generic method for the synthesis of this class of compounds. Boc-protection of (*S*)-**1** lead to (*S*)-**2** in excellent yield and without significant loss of stereochemical integrity (Scheme 2). However, deprotonation of the amide NH with sodium hydride and subsequent alkylation with benzyl bromide lead to the formation of the product (*S*)-**3** with 45 % e.e. (a loss of 40 % e.e.).

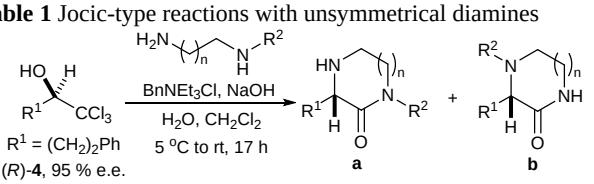


Scheme 2 *Reagents and conditions*: (i) Boc_2O, NaOH, H_2O, rt, 17 h; (ii) NaH, THF, 0 ºC, 90 mins, then BnBr, 0 ºC to rt, 18 h.

We therefore investigated the regioselectivity and enantiospecificity of Jocic-type reactions of enantiomerically enriched trichloromethyl-substituted alcohol (*R*)-**4** (95 % e.e.) with unsymmetrical mixed-primary-secondary 1,2- and 1,3-diamines (Table 1). Generally, as the size of the nitrogen substituent R^2 of the secondary amine increases the formation of 1-substituted piperazin-2-ones is favoured. With R^2 = methyl (entry 2) there is no preference for either the 1- or 4-substituted piperazin-2-one, giving an equal mixture of **7** and **8** in high enantiomeric excess. However, increasing the size of the amine substituent gives a much improved ratio (R^2 = Et, 75 : 25, entry 3), which increases further with R^2 = isopropyl to 95 : 5 (entry 4). We also showed that this reaction worked well with *N*-phenylethylenediamine, which gives the 1-substituted product (*S*)-**12** in 52 % yield and 98 % e.e. (entry 5). It is possible to synthesise substituted diazepan-2-ones **13** and **14** with *N*-benzyl-1,3-propanediamine (entry 6). The formation of the 1-substituted piperazin-2-one may be favoured by the preferential attack of the less sterically encumbered primary amine opening the 2,2-dichloroepoxide.[26] The regioselectivity of related reactions of achiral trichloro-tertiary-alcohols also favours 1-substituted products, but with lower regioselectivity.[26-27] Crystal structures of racemic samples **5**, **6** and **12** confirmed the regiochemistry of

these products (Figure 1). Some 4-substituted isomers (*S*)-**6**, (*S*)-**8** or **14** were independently synthesised by alkylation of the related *N*-unsubstituted piperazinones **1** and **12** or diazepanone **15** [24] in the presence of mild base without deterioration of enantiomeric excess (Table 2).

Table 1 Jocic-type reactions with unsymmetrical diamines



Entry	R	n	Ratio[a] a : b	Yield[b] a	Yield[b] b	e.e.[c] a	e.e.[c] b	Products a	Products b
1	CH_2Ph	1	93 : 7	76	6	94[d]	98	**5**	**6**
2	CH_3	1	50 : 50	46	41	94	96	**7**	**8**
3	CH_2CH_3	1	75 : 25	72	5	96	95	**9**	**10**
4	$CH(CH_3)_2$	1	95 : 5	72	-	99	-	**11**	
5	Ph	1	> 90 : 10	52	-	98	-	**12**	
6	CH_2Ph	2	73 : 27	53	11	99	97	**13**	**14**

[a] by ^{1}H NMR of crude product of racemic reaction; [b] isolated yield; [c] by chiral HPLC analysis; [d] by chiral HPLC analysis on *N*-Boc derivative.

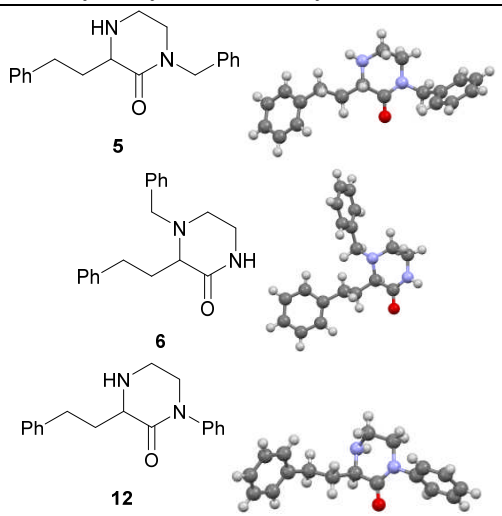
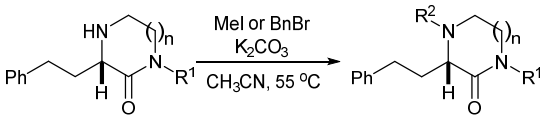


Figure 1 Crystal structures of racemic **5**, **6** and **12** establishing Jocic reaction regiochemistry.

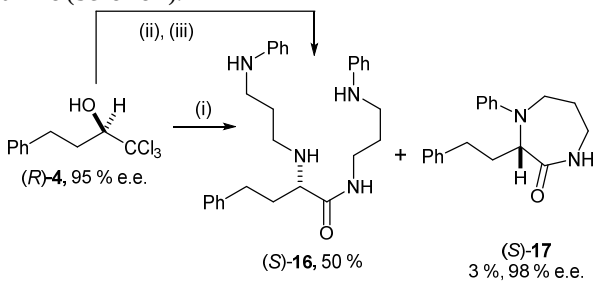
Table 2 Amine-alkylations with mild base.



Entry	R^1	n	S.M.[a]	R^2	Yield[c]	e.e.[e]	Products
1	H	1	(*S*)-**1**	CH_3	37	95	(*S*)-**8**
2	H	1	(*S*)-**1**	CH_2Ph	58	95	(*S*)-**6**
3	H	2	**15**[b]	CH_2Ph	>95[d]	n/a	**14**
4	Ph	1	(*S*)-**12**	CH_2Ph	50	98	(*S*)-**20**

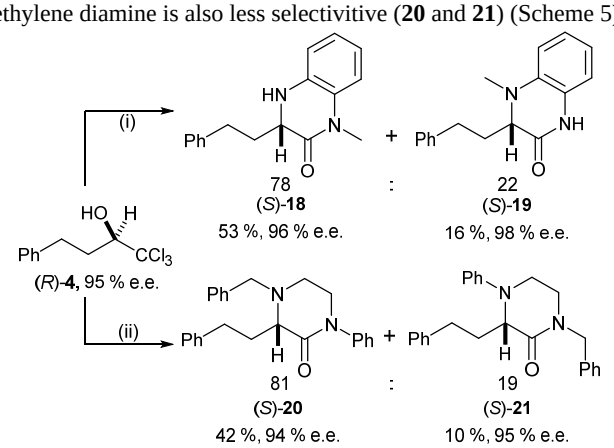
[a] starting material, see table 1 for e.e. [b] racemic starting material; [c] isolated yield; [d] conversion by ^{1}H NMR; [e] by chiral HPLC analysis.

Despite the synthesis of analogous seven-membered lactams often occurring with lower rates of ring closure than six-membered rings,[28] the synthesis of *N*-unsubstituted[24] and 4-benzyl diazepanones (table 1, entry 6) is possible. *N*-Arylation does however significantly impede ring closure in favour of intermolecular amide formation, with no 1-phenyl diazepanone being formed. A trace amount of the 4-phenyl regioisomer was however produced showing that the ring closure of the primary amine is again relatively fast. The unexpected diamine product was independently synthesised using a N^1-protected arylated diamine (Scheme 4).



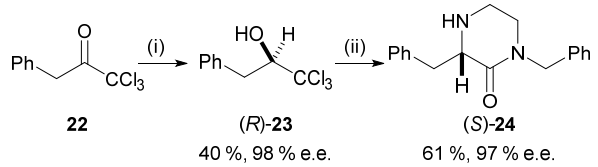
Scheme 4 *Reagents and conditions*: (i) $H_2N(CH_2)_3NHPh$, NaOH, $BnNEt_3Cl$, CH_2Cl_2, H_2O, 17 h, rt; (ii) $H_2N(CH_2)_3N(Ph)CH_2Ph$, NaOH, $BnNEt_3Cl$, CH_2Cl_2, H_2O, 17 h, rt, 18 %; (iii) 10 % Pd/C, HCO_2NH_4, MeOH, reflux, 3 h, 60 %.

A single methyl group provides a small degree of selectivity in the reaction of a phenylenediamine (**18** and **19**), and the relative reactivity of *N*-phenyl and *N*-benzyl ends of an unsymmetrical ethylene diamine is also less selectivitive (**20** and **21**) (Scheme 5).



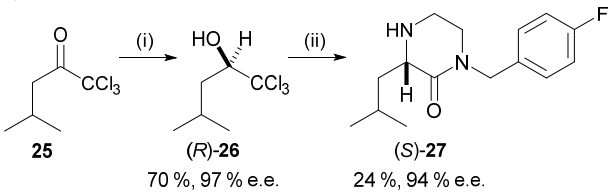
Scheme 5 *Reagents and conditions*: (i) *N*-methyl-1,2-phenylenediamine, NaOH, $BnNEt_3Cl$, H_2O, CH_2Cl_2, rt, 17 h; (ii) as (i) but with N^1-benzyl-N^2-phenyl-1,2-ethylenediamine.

Substituted piperazin-2-ones containing an α-benzyl side chain are present in several medicinally relevant building blocks such as conformationally restricted peptidomimetics.[17c, 17l, 25c, 29] Unfortunately, enantiomerically pure 1,1,1-trichloro-2-phenylpropan-2-ol, the starting material for the Jocic-type reaction, cannot be synthesised via Ru-catalysed asymmetric transfer hydrogenation.[24] However, 1,1,1-trichloro-3-phenylpropan-2-one can be reduced asymmetrically using the CBS catalyst[21a] leading to a general route for the synthesis of compounds such as (*S*)-**24** containing this side chain (Scheme 6). Additionally, we wanted to demonstrate the utility of the reported method using ATH by preparing a key fluorobenzyl intermediate (*S*)-**27** in the synthesis of a PGGTase-I inhibitor (Scheme 7).[6b]



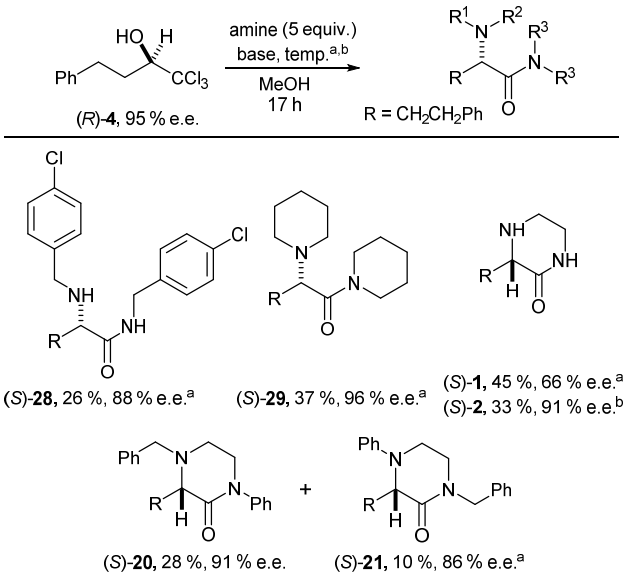
Scheme 6 *Reagents and conditions*: (i) (*S*)-CBS cat. (10 mol %), catecholborane, toluene-THF, - 78 °C to rt, 17 hours; (ii) *N*-

benzylethylenediamine, $BnNEt_3Cl$, NaOH, H_2O, CH_2Cl_2, 0 °C to rt, 17 h.



Scheme 7 *Reagents and conditions*: (a) (*R*,*R*)-TsDPENRu(*p*-cymene)Cl (5 mol %), formic acid/triethylamine (5:2), N_2, 28 °C, 17 h; (d) *N*-4-fluorobenzylethane-1,2-diamine, $BnNEt_3Cl$, NaOH, H_2O, CH_2Cl_2 5 °C to rt, 17 h.

It is known that Jocic / Bargellini reactions that proceed *via* dichloroepoxide intermediates[21k] can also be performed in alcohols instead of chlorinated solvents.[21g, h, 21m, 30] We found that with amine nucleophiles a high, but not perfect, level of stereochemical integrity could be obtained in the amino amide products, however yields are lower than in the biphasic reaction system (Scheme 8).



Scheme 8 *Reagents and conditions*: [a] NaOH (5 equiv.), MeOH, 55 °C, [b] NaOMe (5 equiv.), MeOH, rt.

Conclusions

The stereospecific and sregioselective synthesis of 1-substiuted piperazin-2-ones, where the order of addition of the diamine to the notionally 1,2-*bis*-electrophilic trichloromethyl-alcohol, is controlled by the size of the amine substituent. The good levels of regiocontrol for *N*-benzyl piperazinones is particularly useful as many there are many examples of this substructure are found in compounds with potentially medicinal activity. The reactions in methanol show that this process has some potentially useful possibilities for a simpler mono-phasic system.

Acknowledgements

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Experimental

General Information:

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Advance DRX 250, 300, 400 and 600 MHz spectrometers at room temperature. Chemical shifts are reported in parts per million (ppm) and referenced from $CDCl_3$ (δ_H: 7.26 ppm and δ_C: 77.0 ppm). Coupling constants (*J*) are rounded to the nearest 0.5 Hz. ^1H and ^{13}C assignments were established on the basis of ^1H-^1H COSY, DEPT, HMQC and HMBC correlations. All commercially available solvents and chemicals were used without further purification.

Representative Procedure for Jocic-type Reactions with Amines: *Synthesis of 1-benzyl-3-phenethylpiperazin-2-one* ***5*** *and 4-benzyl-3-phenethylpiperazin-2-one* ***6****:*

(*R*)-1,1,1-Trichloro-4-phenylbutan-2-ol (*R*)-**4** (254 mg, 1 mmol, 1 equiv., 95 % e.e.) and benzyltriethylammonium chloride (4.6 mg, 0.02 mmol, 0.02 equiv.) were stirred in CH_2Cl_2 (1 mL) on ice. *N*-Benzyl-1,2-ethylenediamine (0.75 mL, 5 mmol, 5 equiv.) was added, and the mixture was stirred at 10 minutes before the dropwise addition of NaOH (10 M aq.) (0.5 mL, 5 mmol, 5 equiv.). The reaction mixture was stirred for a further 15 minutes on ice before being allowed to warm to room temperature where it was stirred for 17 hours. Distilled water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica column chromatography (50 % ethyl acetate in 40-60 petroleum ether to 10 % MeOH in ethyl acetate) to give (*S*)-1-benzyl-3-phenethylpiperazin-2-one (*S*)-**5** as a yellow solid (224 mg, 76 %, 94 % e.e.) and (*S*)-4-benzyl-3-phenethylpiperazin-2-one (*S*)-**6** as a yellow solid (18 mg, 6 %, 98 % e.e.). 1-Benzyl-3-phenethylpiperazin-2-one **5**: m.p. 58-61 ºC; ν_{max}/cm^{-1} (neat) 3328 (br. m, NH st.), 1629 (s, C=O st.), 1227 (s, C-N st.); δ_H (400 MHz; $CDCl_3$) 7.36-7.17 (10H, m, Ar*H*), 4.64 (1H, d, *J* 14.5, NC*H*HPh), 4.57 (1H, d, *J* 14.5, NCH*H*Ph), 3.51 (1H, dd, *J* 8.5 and 4, C*H*N), 3.31 (1H, ddd, *J* 11.5, 8.5 and 4.5, C*H*HNBn), 3.16-3.13 (1H, m, C*H*HNH), 3.10-3.06 (1H, m, CH*H*NBn), 2.95 (1H, ddd, *J* 13.5, 10.5 and 5, CH*H*NH), 2.85-2.71 (2H, m, CH_2CH_2Ph), 2.37 (1H, dddd, *J* 14, 10.5, 7 and 4, C*H*HCHCO), 2.03 (1H, dddd, *J* 14, 9.5, 8.5 and 6, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 171.2 (*C*O), 141.6 ($(CH_2)_2ArC_{quat.}$), 136.9 ($NCH_2ArC_{quat.}$), 128.6 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.1 (Ar*C*), 127.4 (Ar*C*), 125.9 (Ar*C*), 58.7 (*C*HN), 50.1 (NCH_2Ph), 47.6 (CH_2NBn), 41.7 (CH_2NH), 34.1 (CH_2CHCO), 32.3 (CH_2CH_2Ph); HRMS (ESI) calc. for $C_{19}H_{23}N_2O$ ($M+H^+$) 295.1805, found 295.1807; $[\alpha]_D^{26}$ = (*c* 0.24, $CHCl_3$): – 52.2. Enantiomeric excess determined by HPLC analysis on *N*-Boc derivative (see ESI). 4-Benzyl-3-phenethylpiperazin-2-one **6**: m.p. 125-127 ºC; ν_{max}/cm^{-1} (neat) 3201 (br., NH st.), 1666 (s, C=O st.), 1494 (m, NH bend); δ_H (400 MHz; $CDCl_3$) 7.28-7.04 (10H, m, Ar*H*), 6.73 (1H, br. s, N*H*), 3.89 (1H, d, *J* 13.5, NC*H*HPh), 3.33 (1H, d, *J* 13.5, NCH*H*Ph), 3.24-3.21 (2H, m, CH_2NH), 3.09 (1H, t, *J* 5, C*H*N), 2.89 (1H, dt, *J* 12.5 and 5,

C*H*HNBn), 2.79 (1H, ddd, *J* 14, 11 and 5.5, CH_2CHHPh), 2.62 (1H, ddd, *J* 13.5, 11 and 5.5, CH_2CHHPh), 2.42 (1H, dt, *J* 12.5 and 6, CH*H*NBn), 2.22 (1H, ddt, *J* 14, 11 and 5, C*H*HCHCO), 2.04 (1H, ddt, *J* 14, 10.5 and 5, CH*H*CHCO); δ_C (100 MHz; $CDCl_3$) 172.4 (*C*O), 142.2 ($(CH_2)_2ArC_{quat.}$), 138.1 ($NCH_2ArC_{quat.}$), 128.8 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 128.3 (Ar*C*), 127.3 (Ar*C*), 125.7 (Ar*C*), 64.1 (*C*HN), 58.2 (NCH_2Ph), 45.0 (CH_2NBn), 39.9 (CH_2NH), 32.0 (CH_2CHCO), 31.4 (CH_2CH_2Ph); HRMS (ESI) calc. for $C_{19}H_{23}N_2O$ ($M+H^+$) 295.1805, found 295.1815; $[\alpha]_D^{26}$ = (c 0.28, $CHCl_3$): – 3.0. Enantiomeric excess determined by HPLC analysis (see ESI).

Notes and references

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† Electronic Supplementary Information (ESI) available: synthesis details, NMR spectra, chiral HPLC chromatograms and crystallographic details. Crystal structures have been deposited at the Cambridge Crystallographic Data Centre and assigned the deposition numbers CCDC 1022612-1022614. See DOI: 10.1039/b000000x/

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