Pergamon

Tetrahedron Letters 44 (2003) 1141–1143

TETRAHEDRON LETTERS

Ring-opening of *N*-alkoxycarbonyl γ-lactams with lithium methylphenylsulphone: application to the synthesis of *cis* 2,5-disubstituted pyrrolidines

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Received 12 November 2002; revised 15 December 2002; accepted 16 December 2002

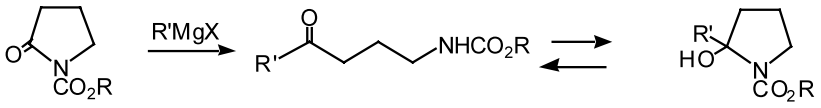
Abstract—The ring-opening of *N*-alkoxycarbonyl γ-lactams with lithium methylphenyl sulphone was studied and applied to the synthesis of enantiopure *cis* 2,5-disubstituted pyrrolidines

The presence of *N*-protecting alkoxycarbonyl (or sulphonyl) groups is well known to enhance considerably the electrophilic character of lactam carbonyl groups, due to their electron withdrawing aptitude. Thus, numerous illustrations of heteronucleophilic attacks at C-2 by hydrolysis or alcoholysis[1] and by aminolysis[2] are reported in the literature. With respect to carbon nucleophilic additions, Grignard reagents opened such pyrrolidin-2-ones leading, in good yield, to an equilibrium of the corresponding acyclic ketones and cyclic quaternary α-hydroxy carbamates as outlined in Scheme 1.[3]

Aryllithium were shown to be also effective in the ring opening of *N*-Boc lactams,[3b,4] but alkyllithium reagents gave generally low yields. Among stabilized carbanions, lithium enolates were reported to react regioselectively in high yield at the γ-lactam carbonyl of *N*-benzyloxycarbonyl pyroglutamates,[5] and methyl *p*-tolylsulphinyl carbanion similarly opened *N*-Boc analog.[6] However, only few examples accounted for the reactivity of methylphenylsulphone anions in nucleophilic addition to activated β-,[7] γ-,[8] and δ-lactam carbonyls.[9] Therefore, we report here the reaction of deprotonated methylphenylsulphones with several functionalized *N*-alkoxycarbonylpyrrolidin-2-ones derived from pyroglutamic acid, and the use of the resulting β-ketosulphones as intermediates in the synthesis of *cis* 2,5-disubstituted pyrrolidines.

The study started with the opening of (*S*)-*tert*-butyl *N*-benzyloxycarbonyl pyroglutamate **1** with deprotonated methylphenylsulphone and the main results are summarized in Table 1.

Nucleophilic addition of lithium anion of methylphenylsulphone (1.28 equiv.) at −72°C afforded the β-ketosulphone **2** in 63% yield, along with some benzenesulphonylacetic acid benzyl ester **3** (13%), due to the attack on the *N*-benzyloxycarbonyl group (Scheme 2, Table 1, entry 1). The ketone **2** was characterized particularly by its NMR spectra (δ H_2-6: 4.11 ppm, δ C-5 (CO): 197.02 ppm). Small amounts (ca. 5%) of the cyclized α-hydroxycarbamate isomer **4** was also observed. By using almost 2 equiv. of the sulphone carbanion, the opening of **1** at the same temperature occurred in 74% yield and **3** was isolated in 21% yield (entry 2).[10] The absence of racemization was indicated by NMR. The enantiomeric excess of **2** was shown to be >95% by ^{1}H NMR spectra in the presence of [Eu(hfc)$_3$] as chiral shift reagent, compared with those of the racemate, and 99% ee was specified by chiral



Scheme 1.

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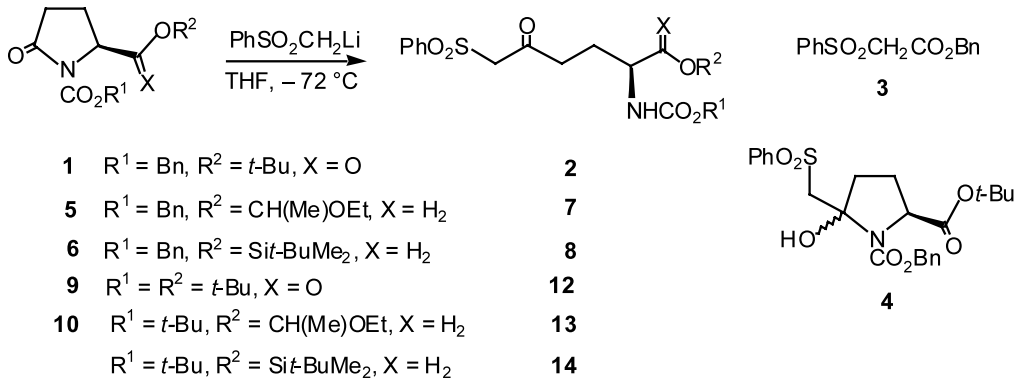
PII: S0040-4039(02)02839-3

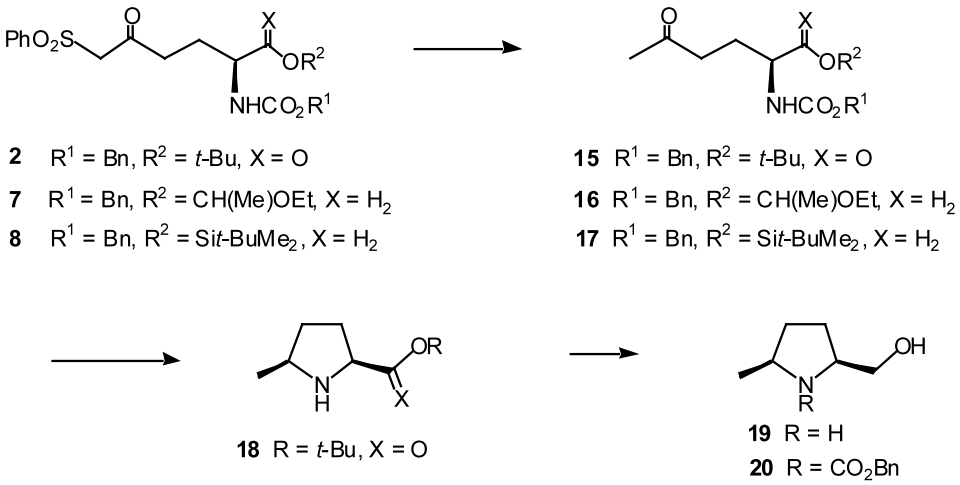
Table 1. Ring-opening of *N*-alkoxycarbonylpyrrolidin-2-ones by methylphenylsulphone carbanion (in THF at −72°C)

Entry	*N*-Alkoxycarbonylpyrrolidin-2-ones	R^1	Nucleophile (equiv.)	β-Ketosulphone (%)	$PhSO_2CH_2CO_2Bn$ (%)
1	**1**	Bn	$PhSO_2CH_2Li$ (1.28)	**2** (63)	13
2	**1**	Bn	$PhSO_2CH_2Li$ (1.94)	**2** (74)	21
3	**5**	Bn	$PhSO_2CH_2Li$ (1.6)	**7** (58)	25
4	**6**	Bn	$PhSO_2CH_2Li$ (1.9)	**8** (62)	18
5	**9**	*t*-Bu	$PhSO_2CH_2Li$ (2.0)	**12** (95)	Not observed
6	**10**	*t*-Bu	$PhSO_2CH_2Li$ (1.85)	**13** (84)	Not observed
7	**10**	*t*-Bu	$PhSO_2CHLi_2$ (1.05)	**13** (55)	Not observed
8	**11**	*t*-Bu	$PhSO_2CH_2Li$ (2.0)	**14** (90)	Not observed



Scheme 2.

HPLC.[11a] The pyrrolidin-2-ones **5** and **6** derived from (*S*)-pyroglutaminol gave similar results, affording **7** and **8**, respectively (entries 3 and 4). Attempts to increase the regioselectivity of the reaction gave only poor results and led us to employ more sterically hindered *N*-Boc protecting group. Accordingly, the compounds **9**–**11**[12] were opened to give the corresponding β-ketosulphones **12**–**14**. In all cases, an excess (ca. 2 equiv.) of monolithium alkylsulphone was needed to obtain high yields (95, 84, and 90%, respectively), owing to the acidity of the resulting β-ketosulphones (Table 1, entries 5, 6, and 8), whereas a more complex mixture was formed in the reaction of **10** with dilithium reagent[13] providing **13** in lower yield (55%, entry 7). Hydrogenation of pyrroline intermediates are known to afford *cis* 2,5-dialkylpyrrolidines and *cis* 5-alkyl prolinates.[14] Thus, in order to develop a stereoselective and efficient route to *cis* 2,5-disubstituted pyrrolidines,[15] the ketone **2** was desulphonylated with 4–5% Na–Hg amalgam leading to **15** in 58% yield and 98.5% ee, as demonstrated by chiral HPLC.[11b] Similarly, desulphonylation of **7** and **8** in the same conditions, afforded the methylketones **16** and **17** (63 and 65%, respectively). The methylketone **15** was subjected to a cyclization–reduction domino sequence under *N*-deprotection conditions (H_2, 1 atm, Pearlman's catalyst, rt) giving rise to **18** (91%) with complete *cis* diastereoselectivity (Scheme 3). The reduction of **18** with $LiAlH_4$ led to the known



Scheme 3.

(2*S*,5*S*)-2-hydroxymethyl-5-methylpyrrolidine **19**,[16a] characterized also as its benzylcarbamate **20**,[16b,17] and these results ascertain the configurations of stereogenic centres.

In conclusion, the opening of *N*-alkoxycarbonyl-protected γ-lactams with lithiated methylphenylsulphone led to functionalized acyclic β-ketosulphones and allowed the preparation of *cis* 2,5-disubstituted pyrrolidines, particularly 5-alkyl prolinate, with high diastereoselectivity. The extension of this methodology to other more complex sulphones, as well as the *cis* introduction by this way of other alkyl groups at C-5, are currently under investigation.

Acknowledgements

We are grateful to Professor J.-Y. Lallemand for a grant (A.J.M.).

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10. *Preparation of* **2**: To a solution of methylphenylsulphone (311 mg, 1.99 mmol) in dry THF (6.0 mL), stirred at −72°C under argon, was added *n*-BuLi (1.6 M solution in hexanes, 1.20 mL, 1.92 mmol). After stirring for 30 min at −72°C, a solution of lactam **1** (316 mg, 0.99 mmol) in THF (4.0 mL) was added dropwise. The mixture was stirred for 1.75 h at the same temperature and a saturated aqueous solution of NH_4Cl (5 mL) was then added. The cooling bath was removed, water (10 mL) was added and the products were extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The residue was purified by chromatography (eluent: heptane–Et_2O–MeOH 50:50:1 v/v) to give compound **3** (61 mg, 21%) and ketosulphone **2** (347 mg, 74%) as a colourless syrup: $[\alpha]_D^{23}$ −6 (*c* 1.40, $CHCl_3$); IR (film): 3366, 2979, 2935, 1722, 1523, 1449, 1369, 1323, 1227, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ (δ ppm = 7.27), *J* (Hz)): δ 7.86 (d, 2H, $J=8$, SO_2Ph), 7.66 (dd, 1H, SO_2Ph), 7.55 (dd, 2H, $J \sim J' = 7$, SO_2Ph), 7.34 (m, 5H, CH_2Ph), 5.38 (bd, 1H, $J_{NH,2}=7.5$, NH), 5.08 (2d, 2H, $J=12$, $PhCH_2$), 4.19 (m, 1H, H-2), 4.11 (s, 2H, SO_2CH_2), 2.78 (m, 2H, H_2-4), 2.15 (m, 1H, Ha-3), 1.82 (m, 1H, Hb-3), 1.45 (s, 9H, *t*-Bu); ^{13}C NMR (75.0 MHz, $CDCl_3$ (centred δ ppm = 77.0)): δ 197.02 (CO), 170.76 (OCO), 156.00 (NCO_2), 138.66 (qC, Ar), 136.18 (qC, Ar), 134.23, 129.29, 128.49, 128.18, 128.05 (CH, Ar), 82.60 (qC, *t*-Bu), 66.93, 66.84 (OCH_2Ph, SO_2CH_2), 53.28 (NCH), 40.06 ($COCH_2$), 27.88 (CH_3, *t*-Bu), 26.46 (C-3); MS (ESI) *m*/*z*: 514 $(M+K)^+$, 498 $[(M+Na)^+$, 100%], 467, 458, 442, 339.
11. (a) HPLC Daicel Chiralcel OD, hexane/ethanol 4/1; (b) HPLC Daicel Chiralcel OD, hexane/2-propanol 9/1.
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17. *Data for* ***19*** *and* ***20***. Compound **19**: $[\alpha]_D^{24}$ +12.7 (*c* 0.70, EtOH), lit.:[16a] +8.8 (*c* 0.4, EtOH); IR (film): 3308 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.69 (bs, 1H, NH), 3.56 (dd, 1H, $J_{a,b}=10.3$, $J_{a,2}=3.8$, $CHaOH$), 3.35 (dd, 1H, $J_{b,2}=5.8$, $CHbOH$), 3.30 (m, 1H, H-2), 3.22 (m, 1H, H-5), 1.82 (m, 2H, Ha-3, Ha-4), 1.57 (m, 1H, Hb-3), 1.29 (m, 1H, Hb-4), 1.13 (bd, 3H, $J=6.2$, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 65.16 (CH_2O), 58.95 (C-2), 54.32 (C-5), 33.35 (C-4), 27.71 (C-3), and 21.81 (CH_3).
Compound **20**: $[\alpha]_D^{23}$ −7.5 (*c* 1.92, $CHCl_3$); IR (film): 3428, 1694, 1681, 771, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 5H, H-Ar), 5.15 (2d, 2H, $J=12.3$, CH_2Ph), 4.61 (bs, 1H, NH), 4.05 (m, 1H, H-5), 3.99 (m, 1H, H-2), 3.72 (bd, 1H, $CHaOH$), 3.60 (dd, 1H, $J_{a,b}=11.2$, $J_{b,2}=7.2$, $CHbOH$), 1.97 (m, 2H), 1.71 (m, 1H), 1.58 (m, 1H), H_2-3 and H_2-4), 1.18 (bd, 3H, $J=5.7$, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 157.38 (NCO_2), 136.45 (qC, Ar), 128.50, 128.04, 127.86 (CH, Ar), 68.20 (OCH_2), 67.25 (OCH_2), 61.99, 54.85 (C-2, C-5), 31.31, 26.75 (C-4, C-3), 21.43 (CH_3); MS (EI) *m*/*z*: 249 ($M^{+\bullet}$), 218, 174, 91 (100%).