Mixed Cyano-Gilman Cuprates – Advances in Conjugate Addition to α,β-Unsaturated Pyroglutaminol

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Abstract: Conjugate addition of lower order cuprates to protected α,β-unsaturated pyroglutaminol 1 is of limited value, mainly due to the requirement for a large excess of the transferable ligand (10 equiv). Here we report advances using mixed cyano-Gilman cuprates which allow the use of only 1.2 equiv of the transferable ligand, to give the desired product in acceptable to good yield (68–84%). Diethyl ether as the solvent was found advantageous versus THF, since the use of TMSCl could be avoided.

Key words: cuprates, lactams, amino acids, addition reactions, asymmetric synthesis

The formation of carbon–carbon bonds by conjugate addition of organocopper complexes to α,β-unsaturated carbonyl systems is a highly valuable and often used synthetic procedure.1 For many years, the term lower order cuprates referred to organocopper complexes derived from addition of two equiv of an organolithium or magnesium reagent to a Cu(I)X salt (X being Br or I). In contrast, organocopper complexes prepared from addition of 2 equiv of an organolithium reagent to Cu(I)CN were named higher order cuprates.2 Quite recently, the role of the cyano group became better understood, and the new term “cyano-Gilman cuprates” was suggested as more appropriate.3 For readily available α,β-unsaturated pyroglutaminol 1,4 the reaction with a lower order cuprate is a well-described synthetic transformation for the preparation of e.g. proline and glutamic acid derivatives. However, it has been established that the use of a large excess of the lower order cuprate ligand (10 equiv) in THF5 or diethyl ether,6 together with the addition of TMSCl, are necessary in order to obtain reasonable yields of the 1-4 adduct to this specific substrate. Here we report advances in using mixed cyano-Gilman cuprates for conjugate addition to α,β-unsaturated pyroglutaminol 1 and that diethyl ether as solvent without addition of TMSCl is superior to THF/2 equiv TMSCl.

In the course of our project on the synthesis of glutamic acid derivatives, we planned a reaction of the known silyl-functionalized lower order cuprate 27 with 1 (Scheme 1), based on previously reported methodology.5 However, the addition of 1 to 5 equiv of 2 at −78 °C led to complete decomposition. Conducting the reaction with only 2 equiv of 2 at −78 °C resulted in full recovery of 1, but upon increasing the temperature to −30 °C, 5a could be isolated in 15% yield from a complex product mixture. Further attempts to optimize the reaction failed. We therefore turned to investigate the use of Cu(I)CN to form the as yet undescribed cyano-Gilman cuprate 3 (Scheme 1). Under optimized conditions, the addition of 1 to 2 equiv of 3 at −30 °C gave full conversion into 5a, which could be isolated in 83% yield. Only one diastereomer could be detected by 1H NMR which is in agreement with other reported observations.5 We also noted that no addition of the cyano-Gilman cuprate 3 to 1 took place at −78 °C.

We were tempted to develop this methodology further, by investigating the potential use of a non-transferable dummy ligand (see Scheme 2). A detailed mechanistic understanding of the lack of transfer of the dummy ligand is not clear at the present time. Originally, selectivity of ligand transfer was thought to arise from tight binding of the dummy ligand to the copper atom. However, recently it was shown that this alone could not account for selectivity and additional coordination of lithium to the non-transferable ligand was suggested to play an important role.8 For our initial studies we chose the 2-thienyl group because of its easy handling, low cost and well-documented useful-

Scheme 1

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An investigation of the mechanistic pathways involved is currently in progress in our laboratory.

All reagents were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone and Et$_2$O was dried over sodium. NMR (300 MHz) spectra were recorded in CDCl$_3$ using CHCl$_3$ as reference. Merck Kieselgel (35–70 mesh) was used for flash chromatography.

2-Lithio thiophene (0.5 M in Et$_2$O–hexanes) To thiophene (0.16 mL, 2 mmol) in anhyd Et$_2$O (2.5 mL) at 0 °C under N$_2$, was added BuLi (1.53 mL, 1.5 M in hexanes, 2 mmol). The reaction was then allowed to stir for 1 h at r.t. and used directly.

Table 1 Reaction of 1.2 equiv of Mixed Cyano-Gilman Cuprates 4a–e with 1 in Et$_2$O

<table>
<thead>
<tr>
<th>Mixed Cyano-Gilman Cuprate</th>
<th>R</th>
<th>5a–e, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>$\text{TMS}$</td>
<td>82%</td>
</tr>
<tr>
<td>4b</td>
<td>$\text{TMS}$</td>
<td>68%$^{12}$</td>
</tr>
<tr>
<td>4c</td>
<td>$\text{LiCN}$</td>
<td>76%</td>
</tr>
<tr>
<td>4d</td>
<td>$\text{LiCN}$</td>
<td>84%</td>
</tr>
<tr>
<td>4e</td>
<td>$\text{LiCN}$</td>
<td>72%</td>
</tr>
</tbody>
</table>

The use of 2-thienyl as the dummy ligand may result in varying degrees of ligand homo-coupling, affording 2,2'-dithiophene. Thus, we explored the potential use of imidazole or pyrrole as dummy ligands.$^{11}$ However, both the lithium bases and the corresponding cyano cuprates of these heterocycles were insoluble in diethyl ether, even at room temperature, preventing their potential use.

In conclusion, we have developed a new methodology for conjugate addition to $\alpha,\beta$-unsaturated pyroglutaminol 1, which is a significant improvement over previously reported methods. The methodology is based on the use of 1.2 equiv of a mixed cyano-Gilman cuprate. We demonstrated that when using mixed cyano-Gilman cuprates, diethyl ether as the solvent is superior to THF, as the use of TMSCl is avoided. The versatility of the procedure was revealed by investigating a variety of structurally diverse cuprates, which all gave the desired product in acceptable to good yield. An investigation of the mechanistic pathways involved is currently in progress in our laboratory.

All reagents were obtained from commercial suppliers and used without further purification. THF was distilled from sodium/benzophenone and Et$_2$O was dried over sodium. NMR (300 MHz) spectra were recorded in CDCl$_3$ using CHCl$_3$ as reference. Merck Kieselgel (35–70 mesh) was used for flash chromatography.

2-Lithio thiophene (0.5 M in Et$_2$O–hexanes) To thiophene (0.16 mL, 2 mmol) in anhyd Et$_2$O (2.5 mL) at 0 °C under N$_2$, was added BuLi (1.53 mL, 1.5 M in hexanes, 2 mmol). The reaction was then allowed to stir for 1 h at r.t. and used directly.

(4R,5S)-1-tert-Butoxycarbonyl-5-(tert-butyldimethylsilyloxy-methyl)-4-(1-trimethylsilyl-2-propen-2-yl)pyrrolidin-2-one (5b) The reaction was carried out as described for 5a but with trans-2,3-trimethylsilylvinylbromide (0.36 mmol).$^{12}$ Purification by flash chromatography (heptane–EtOAc, 9:1) gave pure 5b as a colorless oil (108 mg, 82%).$^{1}$

Analytical data recorded for C$_{21}$H$_{41}$NO$_4$Si$_2$: C, 59.82; H, 9.81; N, 3.17. Found: C, 60.37; H, 9.66; N, 3.54.

Analytical data recorded for C$_{22}$H$_{43}$NO$_4$Si$_2$: C, 59.82; H, 9.81; N, 3.17. Found: C, 60.37; H, 9.66; N, 3.54.

Analytical data recorded for C$_{22}$H$_{43}$NO$_4$Si$_2$: C, 58.97; H, 9.66; N, 3.54. Found: C, 59.30; H, 9.75; N, 3.25.
(4R,5S)-1-tert-Butoxycarbonyl-4-tert-butyl-(5-tert-butyl-dimethylsilyloxymethyl)-pyrrolidin-2-one (5c)

To tert-BuLi (0.36 mmol in Et2O–hexanes) in Et2O (1.3 mL) at –78 °C under N2, was added CuCN (33 mg, 0.36 mmol). The reaction mixture was allowed to warm up to –30 °C (clear solution), then recooled to –78 °C. 2-Lithio thiophene (0.72 mL, 0.36 mmol, in hexanes) was added, and the reaction mixture was allowed to warm up to –30 °C. The flask was cooled to –78 °C and warmed up to –30 °C. The reaction mixture was quenched with sat NaHCO3 and extracted with EtOAc. The organic layer was washed with brine, dried (Na2SO4), and evaporated to give crude 5c. Purification by flash chromatography (heptane–EtOAc, 9:1) gave pure 5c as a colorless oil (88 mg, 76%). [α]25D = –46.7 (c 1.14, CHCl3).

1H NMR: δ = 0.01 (s, 3 H), 0.03 (s, 3 H), 0.86 (br s, 18 H), 1.52 (s, 9 H), 1.95 (br d, 1 H, J = 10 Hz), 2.30 (dd, 1 H, J = 18, 2 Hz), 2.70 (dd, 1 H, J = 18, 10 Hz), 3.58 (dd, 1H, J = 18, 2 Hz), 3.77 (m, 1 H), 3.85 (dd, 1 H, J = 10 Hz), 4.01 (m, 1 H).

13C NMR: δ = –5.76, –5.73, 18.03, 25.70, 26.23, 27.97, 32.66, 34.80, 43.04, 60.59, 64.65, 82.70, 150.07, 174.93.


The reaction was carried out as described for 5e but with phenyllithium (0.36 mmol in Et2O). Purification by flash chromatography (heptane–EtOAc, 9:1) gave pure 5e as a white solid (87 mg, 72%).

(4S,5S)-1-tert-Butoxycarbonyl-4-buty1-5-tert-butyl-dimethylsilyloxymethyl)-pyrrolidin-2-one (5d)

The reaction was carried out as described for 5e but with BuLi (0.36 mmol in hexanes). Purification by flash chromatography (heptane–EtOAc, 9:1) gave pure 5d as a colorless oil (97 mg, 84%). [α]25D = –40.8 (c 0.94, CHCl3).

1H NMR: δ = –0.01 (s, 3 H), 0.01 (s, 3 H), 0.83 (s, 9 H), 0.86 (m, 2 H), 1.47–1.20 (m, 6 H), 1.50 (s, 9 H), 2.07 (dd, 1 d, J = 18, 2 Hz), 2.15 (br q, 1 H, J = 7 Hz), 2.81 (dd, 1 d, J = 18, 9 Hz), 3.65 (dd, 1 d, J = 18, 2 Hz), 3.77 (m, 1 H), 3.85 (dd, 1 d, J = 10, 4 Hz).

13C NMR: δ = –5.78, 13.81, 17.98, 22.36, 25.64, 27.94, 28.82, 33.19, 34.94, 38.63, 63.85, 64.49, 82.67, 150.37, 174.69.

Anal. calcd for C20H39NO4Si: C, 62.29; H, 10.19; N, 3.63. Found: C, 62.40; H, 10.08; N, 3.89.

(4R,5S)-1-tert-Butoxycarbonyl-5-tert-butyl-dimethylsilyloxymethyl)-4-phenylpyrrolidin-2-one (5e)

The reaction was carried out as described for 5e but with phenyllithium (0.36 mmol in Et2O). Purification by flash chromatography (heptane–EtOAc, 9:1) gave pure 5e as a white solid (87 mg, 72%).

1H NMR and 13C NMR gave satisfactory spectra according to the literature.13

Anal. calcd for C22H35NO4Si: C, 65.15; H, 8.70; N, 3.45. Found: C, 65.07; H, 8.65; N, 3.73.

Acknowledgement

We wish to thank Dr. Jeremy Greenwood from Department of Medicinal Chemistry, The Royal Danish School of Pharmacy and Dr. Per-Ola Norrby from Department of Chemistry, The Technical University of Denmark for useful discussions.

References


(4) Preparation of I can be carried out in multigram scale from (S)-glutamic acid. For reference, see: Barrett, A. G. M.; Head, J.; Smith, M. L.; Stock, N. S.; White, A. J. P.; Williams, D. J. J. Org. Chem. 1999, 64, 6005; and references cited therein.


(7) (a) Lower order cuprate 2 was successfully added to cyclohexenone in our laboratory. (b) Trost, B. M.; Coppola, B. P. J. Am. Chem. Soc. 1992, 104, 6879.


(12) The chemical purity of the commercially available trans-2-trimethylsilylvinylbromide was estimated to be approximately 85%.