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Chemoselective reduction of a lactam carbonyl group in the presence of a *gem*-dicarboxylate by sodium borohydride and iodine: a facile entry to *N*-aryl trisubstituted pyrroles

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Abstract—Several *N*-aryl γ-lactam *gem* dicarboxylates were chemoselectively reduced to cyclic amine diesters by using sodium borohydride–iodine system. The reduction in all cases was completed within 2.5 h after refluxing in THF. The cyclic amine products were isolated after aqueous (acidic) workup in good yields. Hydrolytic decarboxylation followed by dehydrogenation produced *N*-aryl carboethoxy pyrroles.

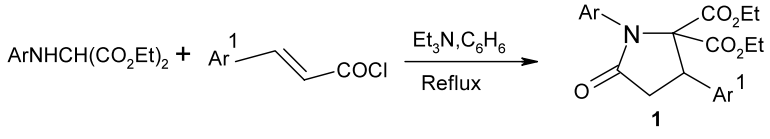
The reduction of a tertiary lactam to the corresponding cyclic tertiary amine is of interest in both natural products[1] and synthetic chemistry.[2] In order to utilize synthetic γ-lactams having two functional groups, viz. lactam carbonyl and ester carbonyl groups, we were eager to develop a methodology which could chemoselectively reduce the carbonyl group of a lactam in the presence of two or more other carbonyl groups preserving the integrity of stereogenic centers in the substrate.

The selectively reduced products were to be utilized for the synthesis of poly substituted pyrrole derivatives which constitute an important class of synthetic pharmaceuticals[3] and natural products with fungicidal and insecticidal activities and which also constitute the building blocks for porphyrin ring systems present in chlorophyll, heme, Vitamin B_{12} and the bile pigments.[4] Additionally, there are a number of pyrrole containing small molecules that exhibit useful biological activities.[5]

Selective reductions of lactam carbonyls in the presence of other reducible groups have usually been accomplished with diborane,[6] 9-BBN (for *N*-alkyl lactams)[7] and $LiEt_3BH/Et_3SiH$-$Et_2O{\cdot}BF_3$ (for *N*-Boc protected lactams).[8] The use of a large excess of $BH_3{\cdot}SMe_2$[9] is reported to reduce lactams in the presence of both esters and carbamates. Various five- and six-membered *N*-alkyl lactams have been reduced (nonselectively) to the corresponding cyclic amines by using lithium *N*,*N*-dialkylaminoborohydrides,[10] but these reagents suffer from disadvantages of cost, inflammability and tedious isolation procedures.

It has been reported that carboxylic acid esters and amides are reduced to the corresponding alcohols and amines using $NaBH_4/ZnCl_2$ in THF[11] in the presence of a tertiary amine and also with $NaBH_4$–I_2 in dry THF[12] under refluxing conditions. The $NaBH_4$–I_2 system is also useful for the chemoselective reduction of lactams in the presence of urethane functionality but with higher reduction times.[13]

In our present work we have synthesized *N*-aryl-3-aryl/heteroaryl-2,2-dicarbethoxypyrrolidines through the



Scheme 1.

Keywords: chemoselective; lactam; reduction; pyrrole.
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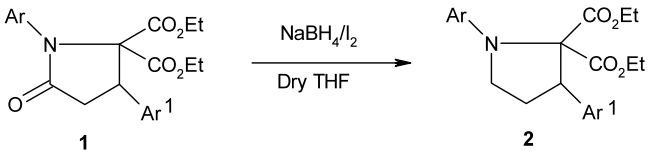

Scheme 2.

highly chemoselective reduction of lactam carbonyls in the presence of geminal diester groups by sodium borohydride and iodine. This serves as a very simple and novel methodology to synthesize bioactive substituted pyrrole derivatives starting from γ-lactam derivatives. The reagent system used is safe, simple and inexpensive.

The γ-lactam diesters **1a–e** were prepared following the general method[14,15] developed in our laboratory. The novel fluoro analogs **1f–j** were synthesized following the same protocol starting from 4-fluoroanilinomalonates and 3,4-difluoroanilinomalonate through intermolecular Michael reactions, followed by intramolecular amide formation (Scheme 1).

The resulting products, on treatment with the sodium borohydride and iodine system in dry THF, furnished substituted pyrrolidines in high yield (Scheme 2 and Table 1).

Even in the presence of excess reagent (7.0 equivalent $NaBH_4$ and 3.5 equivalent I_2) the diester functionality remained unchanged.

By hydrolysis with KOH–H_2O, EtOH, followed by in situ stereoselective decarboxylation of the pyrrolidine **2a**[17a] we synthesized the substituted pyrrolidine monoester **3**, which was converted to the substituted pyrrole derivative **4**[17b] by dehydrogenation using DDQ (Scheme 3).

In conclusion, we have developed a novel method[16] for the chemoselective reduction of lactam carbonyl groups in presence of geminal diesters, in one step, with good yields that will provide a simple and novel approach for the conversion of γ-lactam derivatives to tri-substituted pyrroles.

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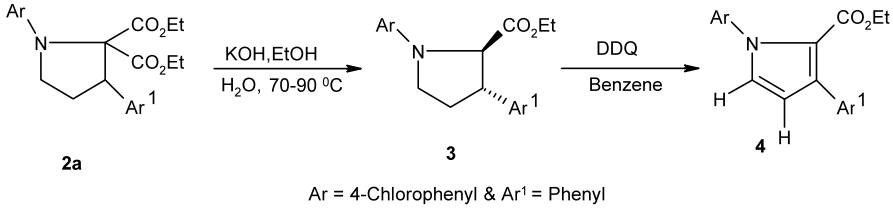
Table 1. Synthesis of pyrrolidines (**2a–j**) from pyrrolidin-2-ones (**1a–j**)

Pyrrolidin-2-one	Ar	Ar^1	Pyrrolidine	Yield (%)
1a	4-Cl-C_6H_4	Phenyl	**2a**	84
1b	4-Cl-C_6H_4	2-Thienyl	**2b**	81
1c	4-Cl-C_6H_4	2-Naphthyl	**2c**	80
1d	4-CH_3-C_6H_4	Phenyl	**2d**	83
1e	4-CH_3-C_6H_4	2-Thienyl	**2e**	77
1f	4-F-C_6H_4	Phenyl	**2f**	83
1g	4-F-C_6H_4	2-Furyl	**2g**	78
1h	4-F-C_6H_4	2-Thienyl	**2h**	78
1i	4-F-C_6H_4	2-Napthyl	**2i**	79
1j	3,4-Difluorophenyl	Phenyl	**2j**	82



Scheme 3.

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16. **General procedure**: To a stirred solution of $NaBH_4$ (4 mmol) in dry THF (20 ml) a solution of iodine (3 mmol) in dry THF (5 ml) was added dropwise under an argon atmosphere at 0°C over 45 min. Next lactamdiester (1 mmol) in dry THF (5 ml) was added to the reagent mixture, which was stirred at 25–30°C for 2 h. Then the mixture was refluxed for 20 min, cooled to 0°C and the excess hydride was carefully destroyed with 3N HCl, neutralized with 3N NaOH. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with sodium thiosulafate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude products were purified by column chromatography. Colourless viscous oily materials were identified by spectroscopic methods.
17. Spectral data of representative compounds.
a. 1-(4-Chlorophenyl)-2,2-dicarbethoxy-3-phenylpyrrolidine (**2a**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (t, 3H, $J\sim7.2$ Hz), 1.16 (t, 3H, $J\sim7.2$ Hz), 2.38–2.57 (m, 2H), 3.64–3.91 (m, 4H), 4.14–4.24 (m, 3H), 6.54–6.62 (m, 2H), 7.09–7.17 (m, 2H), 7.21–7.34 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.49, 13.97, 28.94, 50.07, 55.06, 61.37, 61.84, 115.47, 122.78, 128.22, 128.30, 128.46, 137.88, 144.31, 167.87, 169.40
b. 1-(4-Chlorophenyl)-2-carbethoxy-3-phenyl-1*H*-pyrrole (**4**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H, $J\sim7.1$ Hz), 4.00–4.04 (m, 2H), 6.37–6.38 (d, 1H, $J\sim2.6$ Hz), 6.89–6.91 (d, 1H, $J\sim2.7$ Hz), 7.18–7.20 (d, 2H, $J\sim2.45$ Hz), 7.22–7.24 (d, 2H, $J\sim2.45$ Hz), 7.30–7.53 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.63, 60.24, 111.78, 112.19, 125.55, 127.09, 127.31, 127.64, 127.81, 128.05, 128.87, 129.54, 130.26, 131.90, 132.57, 135.02, 135.56, 140.31, 160.82.