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Highly regioselective rhodium(II)-catalysed carbenoid insertion reaction into sp^2 C–H bond: a general method for the synthesis of 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione ring system

Pranab Haldar, Gandhi K. Kar and Jayanta K. Ray*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

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Abstract—A simple and high yielding general method for the synthesis of 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives through a highly regioselective rhodium(II)-catalysed carbenoid sp^2 C–H insertion reaction on suitably substituted γ-lactam diazocarbonyl compounds is described.

In our ongoing search for novel classes of biologically active heterocycles, we became interested in the exploration of cyclic γ-lactam derivatives as many such compounds[1] have shown antibacterial activity against Gram-positive and Gram-negative bacteria. Tri- and tetracyclic quinolone derivatives fused to a γ-lactam unit have been reported to display DNA-gyrase and topoisomerase-II inhibitory activities.[2]

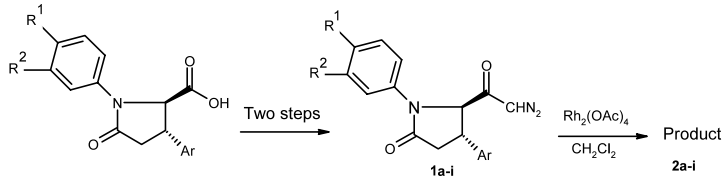
Encouraged by these reports, we aimed to synthesise substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives through an intramolecular Rh(II) carbenoid C–H insertion reaction on suitable diazocarbonyl compounds.

We wanted to use rhodium carbenoid chemistry because, unlike free carbenes, acceptor-substituted carbene complexes often undergo highly regioselective intramolecular C–H insertion into aliphatic and aromatic C–H bonds to generate cyclic compounds.[3]

The required diazocarbonyl compounds **1a**–**d** were synthesised from the corresponding γ-lactam carboxylic acids which, in turn, were prepared following the general method[1,4] developed in our laboratory, through the reaction of their acid chlorides with diazomethane. The novel fluoro analogues **1e**–**i** were synthesised following the same protocol starting from 4-fluoro and 3,4-difluoroanilinomalonates.

These diazoketones **1** when subjected to the rhodium(II) catalysed regioselective sp^2 C–H insertion reaction furnished the substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives in 67–71% yields as the only isolable products (Scheme 1 and Table 1).

The cyclisation was found to be highly regioselective and the insertion reaction took place exclusively in *N*-aryl ring. In addition, for unsymmetrically substituted *N*-aryl groups the regioselectivity is further influenced by the heteroaryl/aryl moiety present at the C-4



Scheme 1.

* Corresponding author.

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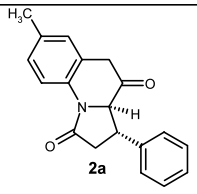
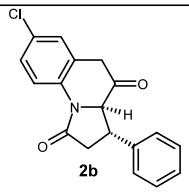
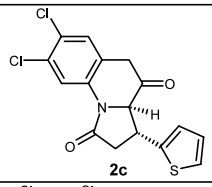
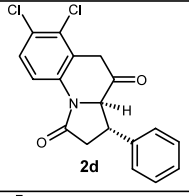
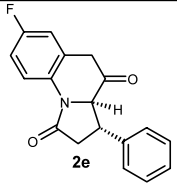
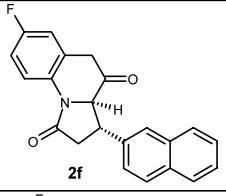
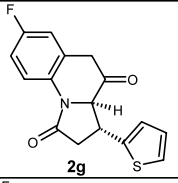
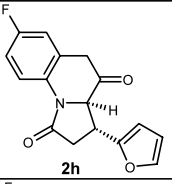
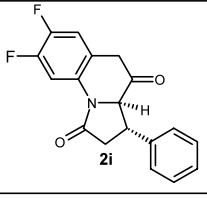
Table 1.

Entry	Substrate	Product	M.P	Yield
1	**1a** (R^1=CH_3, R^2=H, Ar=Ph)	 **2a**	138-140 ^{0}C	71%
2	**1b** (R^1=Cl, R^2=H, Ar =Ph)	 **2b**	156-158 ^{0}C	70%
3	**1c** (R^1=R^2=Cl, Ar=2-thienyl)	 **2c**	144-146 ^{0}C	68%
4	**1d** (R^1=R^2=Cl, Ar=Ph)	 **2d**	148-150 ^{0}C	67%
5	**1e** (R^1=F, R^2=H, Ar=Ph)	 **2e**	152-154 ^{0}C	70%
6	**1f** (R^1=F, R^2=H, Ar =2-naphthyl)	 **2f**	150-152 ^{0}C	68%
7	**1g** (R^1=F, R^2=H, Ar=2-thienyl)	 **2g**	142-144 ^{0}C	69%
8	**1h** (R^1=F, R^2=H, Ar=2-furyl)	 **2h**	134-136 ^{0}C	67%
9	**1i** (R^1=R^2=F, Ar=Ph)	 **2i**	168-170 ^{0}C	69%

of the γ-lactam ring and also by the substituents present in the *N*-aryl moiety. In the case of diazoketones **1c** and **1i**, C–H insertion took place at C-6 (entries 3 and 9) while in case of **1d**, it was found to occur at C-2 of the *N*-aryl moiety (entry 4).

From the above energy minimised form (Fig. 1) of diazoketone **1e**, it was calculated that the distance between the 'CH' of the diazoketone functionality and the *ortho* protons of *N*-aryl moiety were 2.66 and 5.37 Å, whereas the distance with the *ortho* protons of the aryl moiety of the 4-position of the lactam ring were 5.01 and 5.16 Å. As the distance of one *ortho* proton (in the energy minimised locked structure) of the *N*-aryl moiety is much less than to the other *ortho* protons of the aryl moiety, at the 4-position of lactam ring, the C–H insertion is seen to have occurred at the *N*-aryl moiety presumably because of a 'proximity effect'.

All the compounds were characterised by the usual spectroscopic data.

In conclusion, we have developed a simple procedure for the synthesis of novel substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives by highly regioselective intramolecular Rh(II) carbenoid insertion reaction into aromatic C–H bonds. Both the carbonyl groups could be utilised for the further functionalisation of the molecule to synthesise different other substituted γ-lactam derivatives as well as benzoindolizidine derivatives which often have been found to show versatile biological activities.[5]

Typical experimental procedure:

To a stirred solution of diazoketone (1 mmol) in dry dichloromethane (40 ml) a catalytic amount of dirhodium tetraacetate (1 mole%) was added under argon. Stirring was continued at rt (25–30°C) for 3–4 h. After completion of the reaction, the organic layer was washed with water and 3N ice cold HCl. Removal of solvent furnished the crude product, which was purified by column chromatography (silica gel/*n*-hexane-ethyl acetate).

Spectral data of 7-methyl-3-phenyl-3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione **2a**: IR (KBr) ν_{max} 1701 cm^{-1} (br). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.87 (dd, 1H, J=9.4 Hz, 17.5 Hz), 3.04 (dd, 1H, J=9.6 Hz, 17.5 Hz), 3.66 (s, 2H), 3.77–3.90 (m, 1H), 4.22 (d, 1H, J=7.5 Hz), 7.0 (brs, 1H), 7.18 (brd, 1H, J=8.2 Hz), 7.31–7.38 (m, 5H), 7.97 (d, 1H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$): δ 20.8, 38.9, 39.9, 42.4, 69.8, 121.5, 124.9, 127.3, 128.3, 128.8, 128.9, 129.3, 132.0, 135.8, 140.7, 171.0, 205.2.

Acknowledgements

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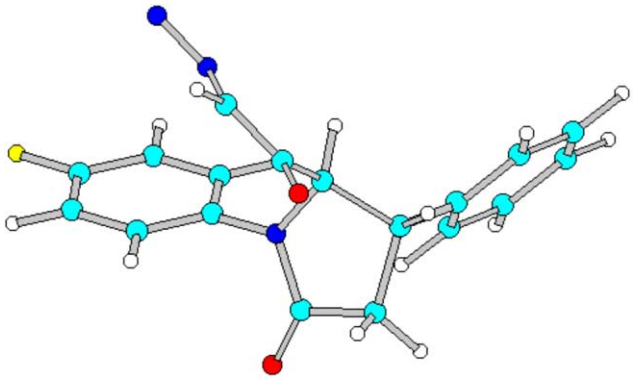

Figure 1. Energy minimised form of diazoketone **1e**.

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