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Synthesis of 6,8-substituted-5,7-difluoro-3,4-dihydro-1*H*-quinoxalin-2-ones via reductive cyclisation of 2,4,6-substituted-3,5-difluoronitrobenzenes

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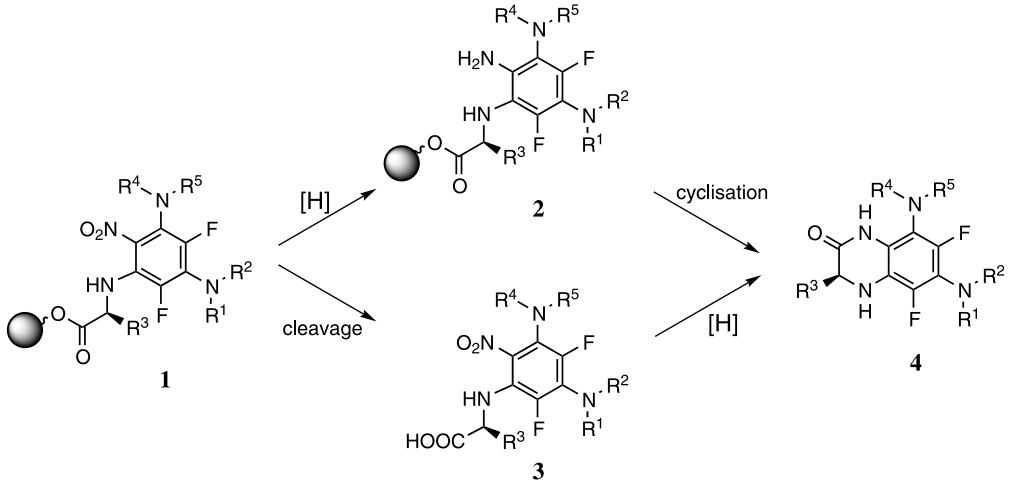
Abstract—The synthesis of substituted 5,7-difluoro-3,4-dihydro-1*H*-quinoxalin-2-ones is described via reductive cyclisation of 2,4,6-substituted-3,5-difluoronitrobenzenes. Reliable conditions for the reduction of solid-phase bound 2,4,6-substituted-3,5-difluoronitrobenzenes were not found. In contrast, solution-phase reductions proceeded smoothly giving the cyclised quinoxalin-2-one products in good yields. A method optimised for rapid parallel synthesis is described, using zinc in acetic acid as reductant, which has been demonstrated to be general for products bearing a range of substituents.

Bicyclic heterocycles such as quinoxalinones, 1,5-benzodiazepin-2-ones and quinazolines are examples of privileged structures which have high importance in combinatorial drug discovery libraries.[1] These heterocycles have been shown to exhibit a diverse range of biological activities as anxiolytics, inhibitors of thymidylate synthase or potent angiotensin II receptor agonists.[2–4] As a consequence, a number of combinatorial library syntheses of these classes of compounds have been reported.[5,6]

In a previous communication, we described the use of pentafluoronitrobenzene as a novel scaffold in the solid-phase synthesis of 2,4,6-substituted-3,5-difluoronitrobenzene libraries **1**.[7] An attractive feature of the pentafluoronitrobenzene scaffold lies in the potential



Scheme 1. Proposed solid-phase or solution-phase synthesis of 6,8-substituted-5,7-difluoro-3,4-dihydro-1*H*-quinoxalin-2-ones **4** from 2,4,6-substituted-3,5-difluoronitrobenzenes **1**.

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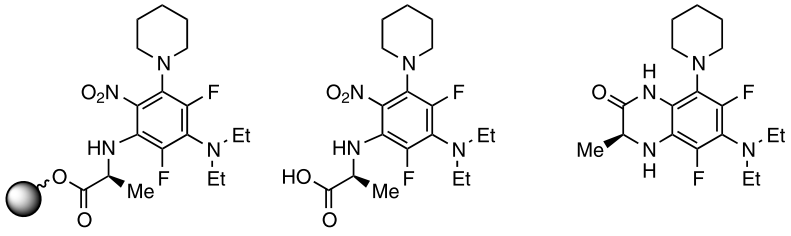
for reduction of the nitro group, thus enabling further modification to the scaffold. The reduction of aromatic nitro groups on solid-phase has been reported by a number of groups under various conditions e.g. $SnCl_2{\cdot}2H_2O$, $Zn/FeCl_3{\cdot}6H_2O$, and Zn/AcOH.[8–10] The formation of a substituted quinoxalinone via intramolecular cyclative cleavage following reduction has been reported to occur in a similar system to ours.[10] We considered that reduction of the solid-supported difluoronitrobenzenes would either give the anilino compound **2** which could be derivatised further, or may result in cyclisation and cleavage from the resin giving the dihydroquinoxalin-2-one **4** (Scheme 1). Alternatively, libraries of dihydroquinoxalin-2-ones **4** could be prepared from **3** in solution by reductive cyclisation following cleavage from the resin as previously described.[7]

The solid-phase reduction was investigated using *N*-3-diethylamino-2,4-difluoro-6-nitro-5-piperidin-1-yl-phenyl-L-alanine HMP ester resin (1% DVB polystyrene) **1a** as a model substrate.[7] LC MS analysis was conducted on the reaction filtrate, and on the reaction product following cleavage from the resin (TFA/DCM). The cyclised product **4a** was observed in the filtrate following reduction under forcing conditions ($SnCl_2{\cdot}H_2O$, DMF, 60°C, 72 h). However, cleavage of the resin following the reaction revealed the presence of significant amounts of unreacted nitro compound **3a**. Reaction with $Zn/FeCl_3{\cdot}6H_2O$, or Zn/AcOH failed to provide the cyclised product. Formation of the uncyclised aniline **2** was not observed under any of the conditions.

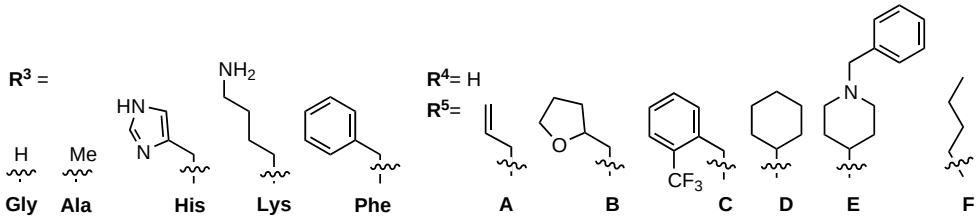
The tin chloride reduction was performed in solution with the corresponding nitro compound **3a** as substrate in order to determine whether the failure of the solid-phase reaction was due to difficulties related to the solid support. In this case the reaction proceeded smoothly to give the dihydroquinoxalin-2-one **4a** in 75% yield.[11]

Representative examples of the perfluoronitrobenzenes **3b–l** were prepared using the solid phase method.[7] Variations of the amino acid (R^3) and the amine substituent (R^4/R^5) *ortho* to the nitro group were expected to be significant. The reduction was initially effected using $SnCl_2$ (5 equiv.) in methanol (reflux, 5 h). The solvent was removed in vacuo and the products analysed (Method A). The results (Table 1) were erratic, with 5 out of 11 examples giving the product in >50% purity and no product being detected in the other reactions possibly due to the excess tin salts present in the crude material. The introduction of a purification



1a **3a** **4a**

Table 1. Reductive cyclisation of substituted difluoronitrobenzenes **3b–l** to dihydroquinoxalin-2-ones **4b–l**



Product	R^3	R^4/R^5	Purity (%)[12]		ESI $[M+H]^+$
4			Method A ($SnCl_2$/MeOH/60°C)	Method B (Zn/AcOH/60°C)	
b	Gly	B	0	64	355
c	Gly	D	68	64	360
d	Ala	A	100	79	459
e	Ala	E	67	85	367
f	His	B	0	65	435
g	His	E	0	71	433
h	Lys	D	0	65	432
i	Phe	C	0	62	520
j	Phe	D	72	76	429
k	Phe	E	0	77	443
l	Phe	F	66	79	417

step at this point was undesirable so a cleaner method of reduction was sought.

The reductive cyclisation of **3a** was repeated using zinc powder in acetic acid (60°C, 2 h), the excess zinc was easily removed by filtration, and the filtrate concentrated in vacuo giving **4a** (87% yield). This method proved to be more robust when performed in parallel on a number of examples (Table 1, Method B), with the desired products **4b–l** being identified in all examples at greater than 62% purity.

In summary, we have used a reductive cyclisation approach to the synthesis of 6,8-substituted-5,7-difluoro-3,4-dihydro-1*H*-quinoxalin-2-ones **4**. Attempts to effect the reduction on the solid-support were not successful. In solution the reaction proceeds smoothly, using a zinc powder and acetic acid couple, and provides the bicyclic heterocycles in good yields. This method is easily amenable to library synthesis and is tolerant to a wide range of substituents around the perfluoronitrobenzene scaffold which are readily prepared using the solid-phase method.

Acknowledgements

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11. Excess tin salts were removed from the crude product by washing with 1:1 NaOH (1 M), DCM.
12. LC MS analysis used gradient elution (MeOH/0.1% HCO_2H), Supelco discovery C18 column (5 cm×4.6 mm). Analysis by UV was recorded at 254 nm. MS was conducted on a Finnigan MAT LCQ in electrospray mode. Purities are based on the peak integral of the crude product peak.