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Reaction of α-amido sulfones with functionalized nitrocompounds: a new two-step synthesis of *N*-alkoxycarbonyl-2,5-disubstituted pyrroles†

Roberto Ballini, Serena Gabrielli,* Alessandro Palmieri and Marino Petrini*

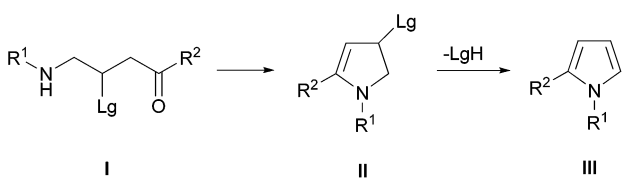
Reaction of α-amido sulfones with nitro ketals promoted by KF on alumina provides the corresponding adducts which, upon treatment with *p*-toluenesulfonic acid, generate the corresponding *N*-alkoxycarbonyl-2,5-disubstituted pyrroles. The latter transformation involves a cascade process including ketal cleavage, ring closure and final aromatization by nitrous acid elimination.

The pyrrole ring occurs frequently in many natural products of paramount importance for their notable bioactivity.[1] Additionally, this nitrogenated heterocyclic system is present in several compounds of synthetic origin known for their antimycobacterial activity and DNA cross-linking properties.[2,3] Pyrrole-containing macrocyclic derivatives are also involved in organic electronic materials and neutral anion receptors.[4,5] The flourishing chemistry associated with pyrrole synthesis has evidenced a plethora of different procedures since the discovery of the Paal–Knorr and Hantzsch reactions.[6] Modern variants of these old-fashioned methodologies involve multicomponent processes which are particularly attractive for their efficiency and eco-sustainability.[7] Several of these new synthetic procedures no longer entail the use of dicarbonyl derivatives for the ring building but exploit other functionalized backbones such as 1,4-dihalodienes,[8] enamides,[9] aminoketones,[10] aminoalcohols[11] and isonitriles.[12]

Intramolecular ring closure of amino derivatives **I**, bearing a carbonyl function in a suitable position of the alkyl framework, represents a viable process for the preparation of pyrrolines **II** (Scheme 1).[13] This strategy can also be settled for the synthesis of pyrroles **III** but would require a tandem elimination process after the ring formation in order to provide the needed aromatic system. To this goal, some synthetic protocols aimed to the efficient preparation of precursors of type **I** have been devised.

In a early work γ-amino ketones **I** (Lg═OH) were obtained by reductive cleavage of isoxazolines which upon reaction with acetic acid were converted into pyrroles **III**.[14] Later on, a procedure involving a Ti(IV) promoted Mukaiyama condensation between silyl enol ethers and azido acetals was employed to prepare γ-azido ketones that, under reductive conditions were converted into polysubstituted pyrroles.[15] More recently, unsubstituted *N*-acylpyrroles have been prepared by acid promoted ring closure of 4-amido-3-methoxy aldehyde dimethyl acetals.[16] Although quite efficient, the latter procedure is affected by poor versatility since only the acyl moiety can be changed in the target products. A common feature of the above cited methods is the utilization of a hydroxy or a methoxy group as leaving group used for the final aromatization step. Knowing the ability of the nitro system in acting as a good leaving group in elimination reactions, we devised a new procedure for the synthesis of *N*-alkoxycarbonyl-2,5-disubstituted pyrroles exploiting a two step strategy as depicted in Scheme 2.[17] α-Amido sulfones **1** are well-known precursors of reactive *N*-acylimines which have been largely involved in nitro-Mannich reactions promoted or catalyzed under basic conditions.[18] For our purpose, the *N*-acylimine is generated from **1** by base-promoted elimination of *p*-toluenesulfinc acid and then attacked by the nitronate anion corresponding to nitro ketal **2** leading to the nitrocarbamate adduct **3**.

In order to test the feasibility of this approach, α-amido sulfone **1a** was made to react with nitro ketal **2a** under various reaction conditions as summarized in Table 1.



Scheme 1 General strategy for the synthesis of substituted pyrroles.

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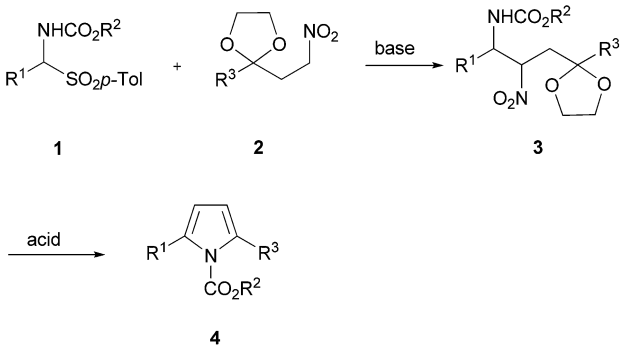
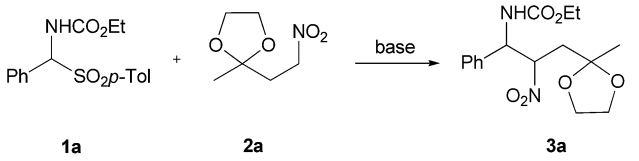
† Electronic supplementary information (ESI) available: General procedures for the preparation of compounds **3** and **4**. Copies of the ^{1}H NMR and ^{13}C NMR spectra for new compounds prepared. See DOI: 10.1039/c4ra08112a



Scheme 2 Synthetic plan for the two-step synthesis of 2,5-disubstituted pyrroles.

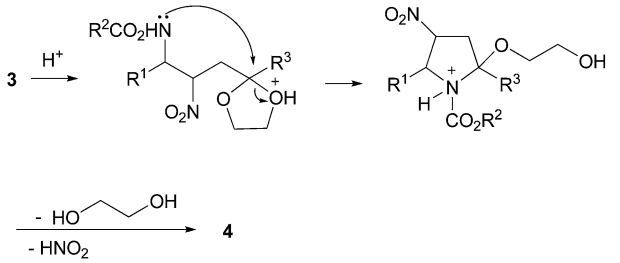
Table 1 Representative optimisation results for **3a**[a]



Entry	Base	Solvent	**3a** Yield[b] [%]
1	NaH	THF	50[c]
2	NaH	THF	89
3	NaH	THF	72[d]
4	Cs_2CO_3	CH_2Cl_2	83
5	KF/Al_2O_3	EtOAc	86

[a] Conditions: **1a** (0.5 mmol), nitroalkane **2a** (1.0 mmol), base (1.5 mmol), rt, 18 h. [b] Yields of isolated products. [c] 1 equiv. **2a** (0.5 mmol) was used. [d] 2 equiv. of NaH were used.

Sodium hydride was the first base used because of its known efficiency in promoting the addition reaction of nitromethane to α-amido sulfones.[19] A preliminary trial using equimolar amount of reactants and 3 equivalents of NaH gave a modest result while a notable increase in the chemical yield was observed doubling the amount of the nitrocompound **2a** (Table 1, entries 1–2). In order to circumvent the problems associated with the utilization of NaH as basic promoter (inflammability, dry conditions *etc.*), another couple of bases working under heterogeneous conditions were tested for our process. Potassium fluoride on alumina and Cs_2CO_3 were proved to be efficient promoters for this addition and after a careful evaluation we decided to employ the former base for all the next reactions.[20] The second step of our protocol for the preparation of 2,5-disubstituted pyrroles **4** entails an acid-promoted cascade process involving a preliminary ketal protonation from compound **3**, followed by ring closure to the intermediate pyrrolidine and a final aromatisation through nitrous acid and ethylene glycol elimination (Scheme 3). An alternative pathway involving direct formation of the carbonyl system, ring closure to the parent 1-pyrroline followed by nitrous acid elimination cannot obviously be ruled out.



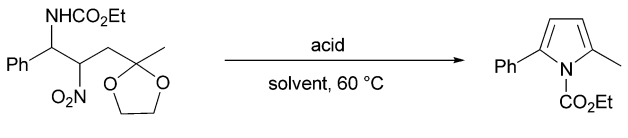
Scheme 3 Proposed mechanism for the formation of pyrrole **4** from nitro ketal **3**.

Because of the superior stability toward cleavage of cyclic ketals over their open chain counterparts, the acidity level of the reaction mixture must be carefully tuned and accounting for the ability of macroreticular sulfonic resin Amberlyst 15 to carry out related processes, this solid acid was initially checked for this purpose (Table 2, entries 1–3).[21]

Reaction of compound **3a** with Amberlyst 15 was proved ineffective in MeOH and only a modest yield of pyrrole **4a** was obtained increasing the solubility of the substrate by adding $CHCl_3$ to MeOH.

Other solid acids were tested for this conversion such as Zeolite HSZ-320 and carbon-sulfonic acid,[22] but only the latter reagent provided encouraging results (Table 2, entries 4–5). Finally, the utilization of *p*-toluenesulfonic acid gave a rather satisfactory yield of pyrrole **4a** when employed in equimolar amount (Table 2, entry 6). Since a reduction of half the amount of acid used resulted only in a negligible decrease in the yield of the obtained pyrrole **4a**, these conditions were selected for the method development. *N*-Alkoxycarbonyl groups in α-amido sulfones **1** other than *N*-ethoxy and *N*-methoxycarbonyl were tested with the aim of providing a possible easier cleavage of the carbamoyl moiety in the final pyrrole **4**. *N*-Benzyloxycarbonyl sulfones **1** (R^2 = Bn) were less reactive than their methyl and

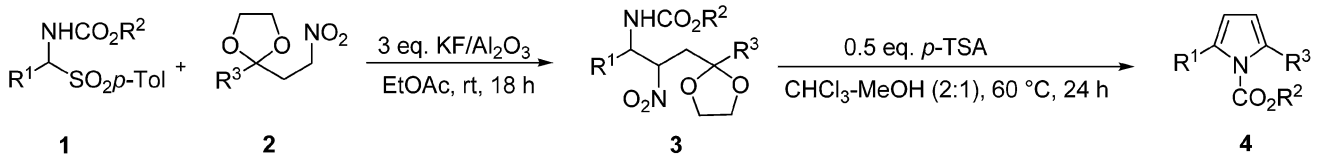
Table 2 Representative optimisation results for pyrrole **4a**[a]



Entry	Acid (g)	Solvent[b]	**4a** Yield[c] [%]
1	Amb 15 (0.5)	MeOH	Trace
2	Amb 15 (0.5)	$CHCl_3$/MeOH	23
3	Amb 15 (1.0)	$CHCl_3$/MeOH	19
4	HSZ-320 (1.0)	$CHCl_3$/MeOH	Trace[d]
5	C-SO_3H (1.0)	$CHCl_3$/MeOH	56[e]
6	*p*-TSA (1.0)[f]	$CHCl_3$/MeOH	72
7	*p*-TSA (0.5)[f]	$CHCl_3$/MeOH	70

[a] Conditions: **1a** (0.5 mmol), acid, 60 °C, 24 h. [b] $CHCl_3$/MeOH, 2 : 1. [c] Yields of isolated products. [d] Zeolite. [e] Carbon-sulfonic acid.[22] [f] Equivalents.

Table 3 Synthesis of *N*-alkoxycarbonyl-2,5-disubstituted pyrroles **4**



1 **2** **3** **4**

Entry	α-Amido Sulfone **1**	R^1	R^2	Nitro ketal **2**	R^3	**3** Yield[a] (%)		Pyrrole **4**	Yield[b] (%)
1	**1a**	Ph	Et	**2a**	Me	**3a**	86	**4a**	70 (53)[c]
2	**1b**	4-NO_2Ph	Et	**2b**	4-MeOPh	**3b**	65	**4b**	55
3	**1b**	4-NO_2Ph	Et	**2a**	Me	**3c**	63	**4c**	84
4	**1c**	4-MeOPh	Et	**2c**	4-*t*-BuPh	**3d**	80	**4d**	55
5	**1d**	Ph	Me	**2c**	4-*t*-BuPh	**3e**	99	**4e**	75
6	**1e**	4-CNPh	Et	**2d**	$Ph(CH_2)_2$	**3f**	97	**4f**	79
7	**1f**	2-FPh	Et	**2e**	1-Hexyl	**3g**	99	**4g**	53
8	**1g**	1-Naphthyl	Et	**2a**	Me	**3h**	67	**4h**	74
9	**1h**	Et	Et	**2f**	Ph	**3i**	90	**4i**	28
10	**1i**	4-FPh	Et	**2g**	Ph(Me)CH	**3j**	95	**4j**	57[d]
11	**1b**	4-NO_2Ph	Et	**2h**	Et	**3k**	88	**4k**	73
12	**1d**	Ph	Me	**2i**	4-MePh	**3l**	72	**4l**	54

[a] Reaction conditions: α-amido sulfone (2.0 mmol), nitro ketal (4.0 mmol), KF/Al_2O_3 (6.0 mmol) in EtOAc (20 mL), at rt, 18 h. Yield of pure isolated product. [b] Reaction conditions: nitrocarbamate (1.0 mmol), *p*-TSA (0.5 mmol), in $CHCl_3$–MeOH (2 : 1, 9 mL) at 60 °C, 24 h. Yield of pure isolated product. [c] Yield in parenthesis refers to the reaction carried out directly on crude **3a** obtained after filtration and evaporation of the solvent calculated on compound **1a**. [d] Reaction time 48 h.

ethyl counterparts in the nitro-Mannich reaction, while nitrocarbamates **3** bearing the *N*-*t*-butoxycarbamoyl moiety (R^2 = *t*-Bu) gave disappointing results in the final step probably because of the acidic conditions affecting the *t*-butyl group.

The optimised conditions found for the two-step transformation were applied to the reaction of different α-amido sulfones **1** with nitro ketals **2** (Table 3). The addition reaction generating the nitro carbamate **3** was quite efficient for most of the combinations tested. The use of the solid base is instrumental in order to simplify the work up operations which involve filtration of the solid base and evaporation of the solvent. The excess of nitro ketal **2** employed, can be almost completely recovered after column chromatography together with the wanted adduct **3**. The subsequent cascade process leading to the pyrrole derivative **4** was rather satisfactory for most of the adducts **3** obtained. For unknown reasons compound **3i** obtained from α-amido sulfone **1h** bearing an alkyl framework gave disappointing results when converted into the corresponding pyrrole (Table 3, entry 9). Conversely, the nature of substituent R^3 in adduct **3** did not affect the outcome of the process so that alkyl or aryl groups can be inserted as substituents in the pyrrole ring. Although isolation of nitrocarbamates **3** is instrumental for the recovery of unreacted nitro ketals **2**, an attempt to use crude nitrocarbamates for the next cyclization step has been pursued in order to evidence possible advantages in the overall process. Crude compound **3a**, obtained by filtration of the basic promoter and evaporation of the solvent, has been used for the next step leading to the formation of pyrrole **4a** in 53% yield based on substrate **1a**. This value is close to that recorded (60%) for the whole process carried out on purified **3a** thus demonstrating that isolation of nitrocarbamates can be avoided with a minimum loss in the overall yield of the target pyrroles **4**.

Conclusions

In conclusion, a novel procedure for the preparation of 2,5-disubstituted pyrrole derivatives has been devised starting from α-amido sulfones **1** which are made to react with nitro ketals **2** in a base promoted addition reaction. The obtained adducts **3** upon treatment with *p*-toluenesulfonic acid undergo to a cascade reaction involving ketal cleavage, cyclization and final aromatization to the target substituted pyrrole. The overall process is featured by a ready availability of the starting materials employed, inexpensive reactants and solvents used, mild reaction conditions and molecular diversity of the substituted pyrroles prepared. Further studies aimed at enlarging the synthetic significance of this procedure to other polysubstituted pyrrole systems are currently underway in our laboratory.

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