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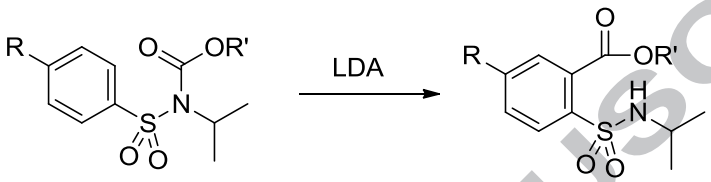

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Intramolecular N-C rearrangements involving sulfonamide protecting groups

Amie Saidykhan[a] , Richard D. Bowen[a], Richard T. Gallagher[b], William H. C. Martin[a]*

[a] *Chemical and Forensic Sciences,University of Bradford, Bradford BD7 1DP, UK*
[b] *Oncology IMED, AstraZeneca, Alderley Park, Macclesfield SK10 4TG, UK*

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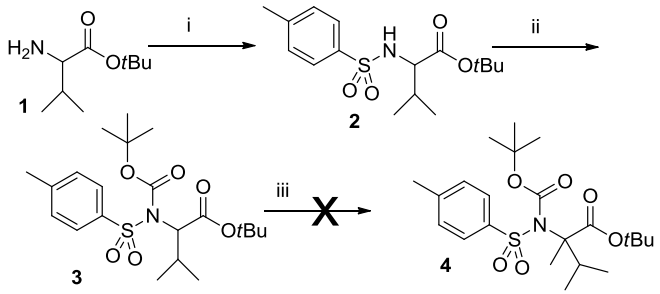
ABSTRACT

The reaction of amine derivatives orthogonally protected with an aryl sulfonamide and a carbamate, *via* a base-mediated nitrogen to carbon rearrangement is reported. This noteworthy isomerisation has implications for the use of sulfonamide protecting groups in synthesis.

Protecting groups and protecting group strategies are an integral part of modern synthetic chemistry.[1] Complex synthesis requires that functional groups are masked for certain synthetic steps, prior to being revealed when reactivity is required at that particular site in the molecule. The requirements that make a good protecting group are well accepted: they should be easy to introduce, inert to subsequent reaction conditions, and then easy to remove. When a robust protecting group is required for nitrogen, sulfonamides are quite often the derivatives of choice. They are straightforward to form from their precursors and are stable to a number of harsh reaction conditions. The *para*-toluenesulfonamide (tosyl) protecting group, for example, is reported to be stable to strong bases such as lithium diisopropylamide (LDA) and, as such, is widely and successfully used in synthetic chemistry.[1] On occasion, however, protecting groups can cease to be bystanders in a reaction, and their reactivity can lead to unwanted, and to the unprepared, unexplained side-products.[2] This communication reports how nitrogen-containing molecules orthogonally protected with a sulfonamide and a carbamate can undergo a base-mediated intramolecular rearrangement involving the sulfonamide protecting group.

As part of a research programme focused on investigating the alkylation of amino acid derivatives, access to an orthogonally substituted amino acid was required.[3] As such, the *t*-butyl ester of valine (**1**) was treated with *para*-toluenesulfonyl chloride to give **2**, which was then converted into its *tert*-butyl carbamate derivative **3** in good yield. With **3** in hand, its low-temperature deprotonation and subsequent alkylation were investigated. However, when **3** was treated with LDA at -78 °C rapid conversion into a more polar material was noted by TLC analysis. The fact that a reaction had occurred before addition of the alkylating agent meant that it was not possible to form **4** using this synthetic pathway; instead a single and unexpected new product had formed (Scheme 1).



Scheme 1: Reagents and conditions: i) *p*-$CH_3C_6H_5SO_2Cl$, Et_3N, CH_2Cl_2, 95% ii) Boc_2O, DMAP, CH_2Cl_2, 78%, iii) LDA, THF, MeI, -78 °C

This unexpected product was subjected to spectral analysis to determine its structure. The FTIR spectrum contained a strong peak at 1718 cm^{-1}, indicative of the C=O stretch of an aromatic ester. The ^1H NMR spectrum showed the absence of one proton *ortho* to the sulfonamide group of the benzene ring, and an HMBC experiment gave a correlation between an ester carbon and the proton in the benzene ring *ortho* to the methyl in the benzene ring (Figure 1). High-resolution ESI^+ mass spectrometry (on the prominent MH^+ ion) established that the product had the

* Corresponding author. Tel.: +441274233362; e-mail: wmartin@bradford.ac.uk

same molecular formula ($C_{21}H_{33}NO_6S$) as **3**. These data indicated that a rearrangement had occurred to give the ester, **5**.

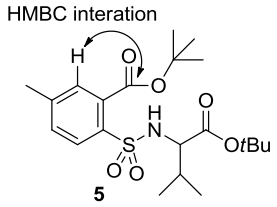


Figure 1: HMBC confirming the structure of compound **5**.

Evidence for the possible mechanism by which the product was formed was found in the following observations: a single regioisomer of the product was isolated, in which a new ester moiety was positioned *ortho* relative to the existing sulfonamide linkage, and LDA is not a strong enough base to deprotonate the aromatic ring directly. These factors point towards a directed *ortho* metallation (DOM) having occurred.[4] As such, deprotonation of **3** could give rise to chelated structure **6**, where the incipient anion is stabilised by the sulfonamide and/or the carbamate. Rearrangement of this intermediate would then give the observed product **7** (Scheme 2).

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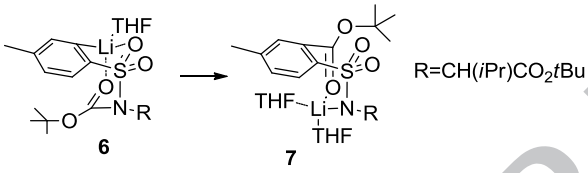
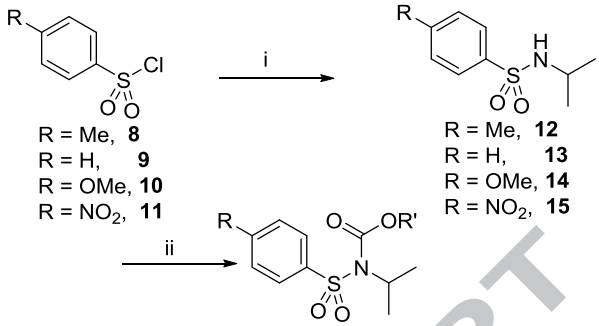


Scheme 2: Possible mode by which DOM could occur in compound **3**.

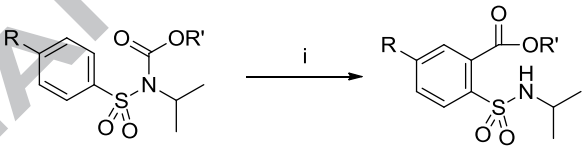
Although sulfonamides are known to be strong activators for DOM reactions,[5,6] intramolecular nitrogen to carbon transfer of an electrophile has not, as far as has been ascertained from the literature, been reported in systems such as those presented here. As such, the fact that an intramolecular rearrangement has been effected by LDA in the present case is noteworthy and will need to be considered when planning a protecting group strategy in substrates of this kind.

The generality of the rearrangement was then explored by synthesising a number of orthogonally protected isopropylamines. Treatment of isopropylamine with the corresponding sulfonyl chloride **8**-**11** gave the sulfonamides **12**-**15** in excellent yields. Each of the sulfonamides was then converted into either their *tert*-butyl, ethyl or methyl carbamates to give compounds **16**-**19**, **20**-**23** and **24**-**27**, respectively, all in good yield (Scheme 3).



Scheme 3: Reagents and conditions: i) *i*-PrNH$_2$, Et$_3$N, CH$_2$Cl$_2$, ii) LDA, THF, R′OCOCl, -78 ^oC.

The orthogonally protected isopropylamine derivatives were treated with LDA at -78 ^oC. Sulfonamides with a *para*-methyl and *para*-methoxy group, and those based on benzenesulfonamide itself, showed rapid conversion (less than 10 minutes) to give the corresponding aromatic ester derivatives. Intriguingly, the *para*-nitrosulfonamide (nosyl) derivatives showed no reaction and unreacted starting material was recovered (Scheme 4, Table 1).



Scheme 4: Reagents and conditions: i) LDA, THF, -78 ^oC

Entry	Substrate	Product	R	R′	Yield (%)
1	**16**	**28**	Me	*t*Bu	85
2	**20**	**29**	Me	Et	78
3	**24**	**30**	Me	Me	83
4	**17**	**31**	H	*t*Bu	92
5	**21**	**32**	H	Et	78
6	**25**	**33**	H	Me	84
7	**18**	**34**	OMe	*t*Bu	90
8	**22**	**35**	OMe	Et	93
9	**26**	**36**	OMe	Me	80
10	**19**	--	NO_2	*t*Bu	No reaction
11	**23**	--	NO_2	Et	No reaction
12	**27**	--	NO_2	Me	No reaction

Table 1

The fact that the *para*-nitrosulfonamides (entries 10, 11 and 12, Table 1) were stable under the reaction conditions, and gave unreacted starting material was surprising. On first inspection, it might be supposed that the electron-withdrawing group would stablise the anion formed by deprotonation of the aromatic ring. Indeed, a colour change to give a deep-yellow solution was noted upon addition of LDA to the *para*-nitrosulfonamide derivatives, a colour transition that is normally associated with deprotonation

of the substrate. The possibility that the nosyl derivatives were being deprotonated *ortho* to the nitro group leading to an unreactive anion that could not undergo intramolecular rearrangement was investigated. Compound **24** was treated with LDA at -78 ^{o}C, and was then immediately quenched with D_2O; no incorporation of deuterium in the recovered sulfonamide was observed. The fact that the nosyl group is inert to the reaction conditions, whilst being difficult to explain, presents a solution to the protecting group incompatability issue identified in this communication.

In conclusion, it has been shown that orthogonally protected amines where one of the protecting groups is a sulfonamide and the other a carbamate are susceptible to base-induced rearrangement. However, the *para*-nitrosulfonamide (nosyl) protected amines did not undergo this rearrangement. This leads to the important conclusion that in situations where rearrangement might be a problem that the nosyl protecting group should be the protecting group of choice.

Acknowledgments

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References and notes

1. Kocienski, P. J., *Protecting Groups 3rd edition*, Thieme: Stuttgart, **2000**.
2. Rushingwa, E.; Touray, H. K.; Bowen, R. D.; Gallagher, R. T.; Martin, W. H. C., *Tetrahedron Lett*., **2013**, *54*, 4726.
3. Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Int. Ed. Engl*., **2000**, *39*, 2155.
4. Fu, J. M.; Zhao, B. P.; Sharp, M. J.; Snieckus, *V. J. Org. Chem*. **1991**, *56*, 1683.
5. Ould Aliyenne, A.; Khiari, J. E.; Kraiem, J.; Kacem, Y.; Hassine, B. B., *Tetrahedron Lett.*, **2006**,47, 6405
6. Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, X. J. G.; Nanninga,T. N.; Risedorph, G. S.; Seamans, R.E.; Skeean, R.; Winkle, D. D.; Zennie, T. M., *Org. Process Res. Dev*., **2004**, *8*, 201-212

Supplementary Material

General experimental procedures and full experimental data for all new compounds are provided.