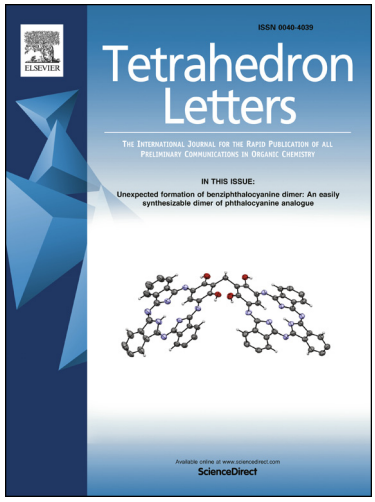


The scope and regioselectivity of intramolecular N-C rearrangements of orthogonally protected sulfonamides, including cyclization to saccharin derivatives

Amie Saidykhan, Jenessa Ebert, Hashim Ally, Richard T. Gallagher, William H.C. Martin, Richard D. Bowen

PII: S0040-4039(17)30784-0
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.06.053
Reference: TETL 49045

To appear in: *Tetrahedron Letters*

Received Date: 17 March 2017
Revised Date: 12 June 2017
Accepted Date: 16 June 2017

Please cite this article as: Saidykhan, A., Ebert, J., Ally, H., Gallagher, R.T., Martin, W.H.C., Bowen, R.D., The scope and regioselectivity of intramolecular N-C rearrangements of orthogonally protected sulfonamides, including cyclization to saccharin derivatives, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.06.053

Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

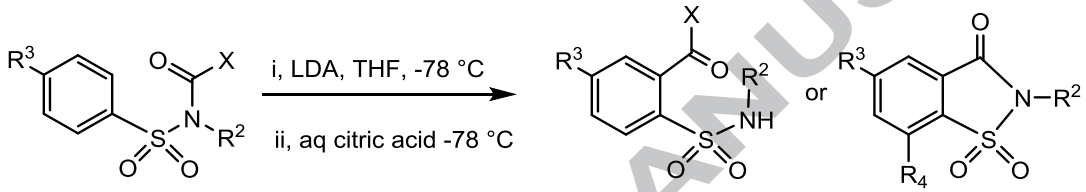
Leave this area blank for abstract info.

The scope and regioselectivity of intramolecular N-C rearrangements of orthogonally protected sulfonamides, including cyclization to saccharin derivatives

Amie Saidykhan,[a] Jenessa Ebert,[a] Hashim Ally,[a] Richard T. Gallagher,[b] William H. C. Martin[a] and Richard D. Bowen[a,*]

[a] School of Chemistry and Forensic Sciences, Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK

[b] Oncology IMED, AstraZeneca, Alderley Park, Macclesfield, SK10 4TG, UK



X = OMe, O*t*Bu, *i*Pr, *i*Bu, *neo*C_5H_{11}, *t*Bu;
R^2 = Me, *i*Pr; R^3 = Me or Ac.

When $R^4 \neq H$

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

The scope and regioselectivity of intramolecular N-C rearrangements of orthogonally protected sulfonamides, including cyclization to saccharin derivatives

Amie Saidykhan,[a] Jenessa Ebert,[a] Hashim Ally,[a] Richard T. Gallagher,[b] William H. C. Martin[a] and Richard D. Bowen[a,*]

[a] School of Chemistry and Forensic Sciences, Faculty of Life Sciences, University of Bradford, Bradford BD7 1DP, UK

[b] Oncology IMED, AstraZeneca, Alderley Park, Macclesfield, SK10 4TG, UK

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Protecting groups
Sulfonamides
Rearrangement
Deprotonation
Synthetic strategy
Protection

ABSTRACT

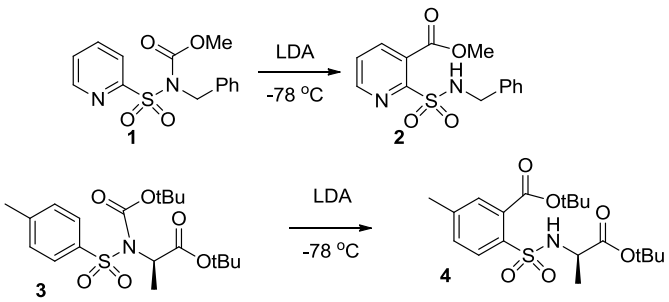
The scope and regiochemistry of the intramolecular N-C rearrangement involving ortholithiation of orthogonally protected sulfonamides in which an N-acyl or N-carboalkoxy group is transferred from nitrogen to the aromatic ring have been explored. Provided that excess lithium diisopropylamide is used, the process is compatible with the presence of acidic α-protons in a substituent attached to the aromatic ring or if the protons in the migrating acyl group are relatively inaccessible because of steric factors. In certain cases, the isolated product is not the ortho carboalkoxyl species, but the derived saccharin; the regiochemistry found for starting materials containing a naphthalene ring is consistent with ortho lithiation at the most electron deficient position.

Aryl sulfonamides are important moieties that are found in several biologically active molecules, examples of which are utilized in the pharmaceutical and agrochemicals industries.[1-3] Aryl sulfonamides are also used extensively in organic synthesis, with the para-toluenesulfonyl (tosyl) group in particular frequently being employed as a protecting group on nitrogen.[4]

Recently we reported a nitrogen to carbon base-catalysed rearrangement that gives access to aryl sulfonamides substituted in the 2-position (eg, **1** to **2**, Scheme 1).[5,6] This novel rearrangement, which bears some resemblance to the acyl transfers that occur in imides,[7] was initially exploited to prepare a number of aryl and heteroaryl sulfonamides with acyl and carboalkoxy substituents in the aromatic ring.[5] Subsequently, we reported that this rearrangement can complicate the reactions of orthogonally protected amino acids, where migration of a carboalkoxy substituent from nitrogen to the tosyl protecting group may lead to unwanted side products when these substrates are subjected to basic conditions (eg, **3** to **4**, Scheme 1).

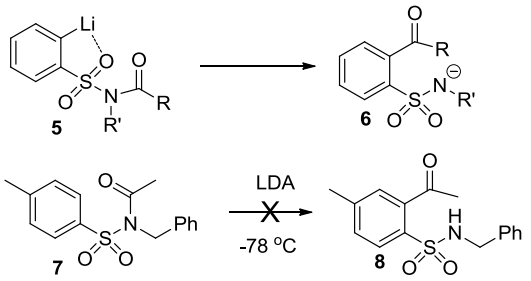
The rearrangement was done in tetrahydrofuran at low temperatures (-78 °C) with lithium diisopropylamide (LDA). When tlc showed complete consumption of the starting material, the reaction was quenched with saturated aqueous citric acid solution at -78 °C. Details of a typical procedure are given in the supplementary information.

Attempts to use BuLi directly failed because the anion behaved as a nucleophile rather than as a base. Similarly, the rearrangement could not be performed satisfactorily at higher temperatures. The absence of crossover products when two different substrates were treated together with LDA indicated that this rearrangement is intramolecular, rather than intermolecular, in nature.



Scheme 1: Nitrogen to carbon acyl migration in sulfonamide derivatives. Reagents and conditions: LDA (1-2 equivalents), -78 °C, 60-80%.

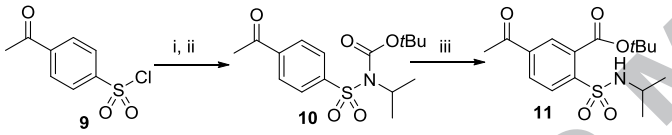
The proposed reaction mechanism invokes Directed Ortho Metallation (DOM), as aryl sulfonamides are known to be strong DOM directing groups that promote lithiation at the *ortho* position, which in the current case would lead to the lithiated intermediate **5**.[8-10] This species then undergoes an intramolecular rearrangement in which the N-acyl or N-carboalkoxy group is transferred from nitrogen to carbon to give **6** (Scheme 2). The driving force for this rearrangement is thought to reflect the relative stability of the final nitrogen based anion compared to the previous intermediate in which the formal anionic site is on carbon.



Scheme 2: DOM and incompatibility with acidic protons

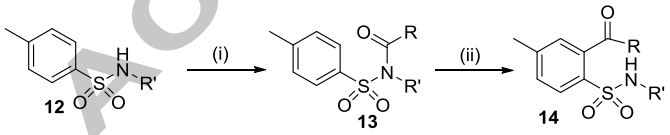
The initial study[5] indicated that simple transfer of an acetyl group was not possible: attempted rearrangement of the sulfonamide **7** did not give the desired product **8** (Scheme 2). This finding suggested that the presence of groups containing an additional (more) acidic proton might prevent the rearrangement, because deprotonation of the migrating group would convert the carbonyl group into an enolate and reduce its electrophilicity.

In order to investigate the influence of acidic protons remote from the migrating group, the 4-acylsulfonamide, **10**, was prepared. When treated with excess LDA at -78 °C, clean conversion to the rearranged product **11** occurred (Scheme 2). Therefore, the presence of acidic protons in groups attached to the aromatic ring does not necessarily prevent rearrangement, provided that excess LDA is employed.



Scheme 3: Reagents and conditions: i) *i*-$PrNH_2$, Et_3N, CH_2Cl_2 -5 °C, 99% ; ii) BOC_2O, DMAP, py, rt, 60%; iii) LDA (3 equivalents), -78 °C, 99%.

The scope of the rearrangement was further extended by investigating higher homologues of **7** that contain protons on the α-carbon atom of the acyl group which might either migrate or be deprotonated. A series of compounds in which the level of steric hindrance to deprotonation of the α-carbon atom was progressively increased was prepared. Treatment of the acyl derivative **13** under the standard conditions for rearrangement then either gave the rearranged product **14** or decomposed the starting material (Scheme 4 and Table 1).



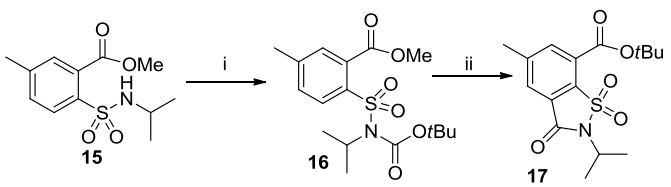
Scheme 4: Reagents and conditions: i) NaH, THF, R'OCOCl, 0 °C – rt; iii) LDA, (3 equivalents), -78 °C. See Table 1 for yields.

Entry	R^1	R	**14**	**13**
i	CH_3	CH_3	0	78
ii	CH_3	$CH_2CH_2CH_3$	0	83
iii	CH_3	$CH(CH_3)_2$	98	0
iv	CH_3	$CH_2CH(CH_3)_2$	46	0
v	CH_3	$CH_2C(CH_3)_3$	55	0
vi	$CH(CH_3)_2$	CH_3	0	90
vii	$CH(CH_3)_2$	$CH_2CH_2CH_3$	0	92
viii	$CH(CH_3)_2$	$CH(CH_3)_2$	68	0
ix	$CH(CH_3)_2$	$CH_2CH(CH_3)_2$	65	0
x	$CH(CH_3)_2$	$CH_2C(CH_3)_3$	50	0
xi	CH_3	$C(CH_3)_3$	46	0

Table 1: The effect of varying the structure of R

The data of Table 1 reveal that the nature of the group that may migrate has a profound effect on the competition between rearrangement and decomposition of the starting material. The rearrangement may be successfully induced in certain cases despite the presence of additional acidic protons. When the acyl group contains an unbranched alkyl group (such as *n*-propyl), decomposition of the starting material occurred, as was previously observed for the archetypal homologue with an acetyl group.[5] In contrast, branching at the α- or β- carbon atom (where the acyl substituent contains an isopropyl, isobutyl or neopentyl group, respectively, that would be expected to offer a significant steric obstacle to deprotonation by a large base), favours transfer of the acyl group to the ortho position. In these more hindered systems, clean transfer of the *i*C_3H_7CO, *i*C_4H_9CO or *neo*$C_5H_{11}CO$ substituent occurred, without decomposition of the starting material. As was initially reported,[5] transfer of acyl substituents, such as *t*C_4H_9CO, which do not contain acidic α-protons, is easily achieved. The discovery that acyl groups in which the acyl substituent has one or two relatively inaccessible acidic α-protons may be transferred from nitrogen to the aromatic ring further expands the scope of this rearrangement, which may involve reversible metallation and/or interconversion of isomeric anions or dianions, as has been observed for *N*,*N*-diethylbenzamides.[8]

The possibility of conducting a second rearrangement to give a sulfonamide product substituted in both ortho positions of the aromatic ring was also explored. To this end, the product after one rearrangement, **15**, was elaborated with methyl chloroformate and sodium hydride to give **16**, which was then subjected to another rearrangement in the usual way. The ^1H NMR spectrum of the product, **17**, showed that ring closure to form a saccharin derivative had taken place (Scheme 5).

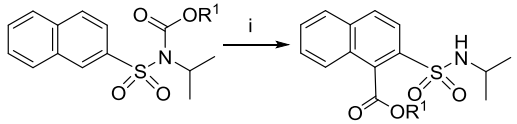


Scheme 5: Reagents and conditions: i) BOC_2O, DMAP, py, 92%; ii) LDA, 1.5 equivalents -78 °C, 64%.

Saccharin derivatives had not previously been identified as products of this rearrangement. However, in sterically hindered

systems such as **17,** preference for the saccharin product comes into effect. Saccharin derivatives have previously been prepared by metallation of sulfonamides,[9-12] however, the current route is potentially useful because ring closure of the parent ester (which would be formed by migration of the carboalkoxy group to the aromatic ring) normally requires elevated temperatures.[13]

In order to probe the regiochemical preferences of the rearrangement in more complex aromatic systems, the naphthalene analogues **20-23** were prepared and investigated. The migration terminus for rearrangement of the 2-substituted naphthalenes, **18** and **19**, could be either the 1 or the 3 position. The ^{1}H NMR spectra of **18** and **19** contained a distinctive singlet at lowest chemical shift (δ 8.45 and 8.42 ppm, respectively), assigned to the proton in the 1 position. No such signal was present in the ^{1}H NMR spectra of the rearrangement products, **20** and **21**. Consequently, **20** and **21** must be 1,2-derivatives, formed by migration of the CO_2R group to the 1-position (Scheme 6). As would be expected intuitively, studies of naphthalene derivatives have established that metallation usually occurs in the position and ring in which the electron density is lowest.[10,14,15] Therefore, the metallation of **18** and **19** at the 1-position, leading to **20** and **21**, respectively, is consistent with earlier results.[16,17]

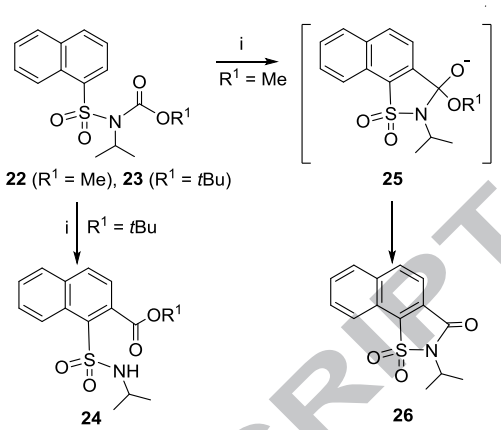


18 (R^1 = Me), **19** (R^1 = *t*Bu) **20** (R^1 = Me), **21** (R^1 = *t*Bu)

Scheme 6: Reagents and conditions: i) LDA (2 equivalents), -78 °C, 70%.

Parallel results were obtained for the 1-substituted species, **22** and **23**, for which rearrangement to either the 2 or 8 ("peri") position could occur. Treatment of **22** with excess LDA (2 equivalents) under standard conditions gave the 1,2-disubstituted product, **24**: the ^{1}H NMR spectrum of this product showed a singlet at 1.70 ppm and a doublet at 4.92 ppm, which were assigned to the *t*-butyl and NH group, respectively (Scheme 7). Similar behaviour was observed for **23**, but the isolated compound was not the 1,2-disubstituted product, but the derived saccharin analogue, **26**. The regiochemistry of this rearrangement is generally consistent with literature precedent: metallation would be expected to occur at the 2-position because this ring has the sulfonamide substituent (and is, therefore, less electron rich than the unsubstituted ring) and is "ortho" to the sulfonamide group.[11,14-16]

A plausible mechanism by which a saccharin analogue could be formed from **22** is direct elimination of a methoxide anion from the tetrahedral intermediate, **25** (Scheme 7). The formation of a saccharin analogue from the intermediate tetrahedral anion formed from **23** would entail elimination of a *t*butoxy anion, which is a distinctly poorer leaving group than a methoxy anion.



Scheme 7: Reagents and conditions: i) LDA (2 equivalents), -78 °C, 60-75%.

The formation of a saccharin analogue from **22**, but not **18**, may be explained in terms of the general influence of steric factors in the reactions of naphthalene derivatives. Unfavourable interaction between the $SO_2NiC_3H_7$ entity, which has a considerable steric requirement, with the "peri" hydrogen atom will tend to favour elimination of methoxide to form the saccharin analogue, in which steric crowding will be less pronounced than in the product with SO_2NHiPr and CO_2CH_3 substituents in the 1 and 2 positions. In contrast, the corresponding steric effects in **18** arising from interaction of the "peri" hydrogen atom with the much smaller CO_2CH_3 substituent, are far less pronounced. Consequently, there is no longer a thermodynamic driving force for cyclisation. The fact that **23** does not undergo cyclisation, despite possessing a larger CO_2*t*Bu substituent, is explicable because expulsion of *t*butoxide is unfavourable.

In conclusion, four further useful discoveries have been made about the scope and regioselectivity of the nitrogen to carbon rearrangement of orthogonally protected sulfonamides. Firstly, the rearrangement may be induced even when a substituent that could be deprotonated under the reaction conditions required for the acyl or carboalkoxy transfer is attached to the aromatic ring, provided that excess lithium diisopropylamide is employed, so as to deprotonate the other group and facilitate ortho metallation. Secondly, acyl substituents containing acidic α-protons may be caused to migrate, provided that these protons are flanked by branched alkyl groups. Thirdly, sequential migration of two substituents can be effected; moreover, spontaneous cyclisation of the intermediate species sometimes occurs to form a saccharin derivative, which would otherwise be accessible only under more forcing conditions. Fourthly, essentially regiospecific migration of a carboalkoxy group in naphthalene systems is possible to the electron deficient ring to which the sulfonamide substituent is attached. These discoveries substantially enhance the synthetic utility of this novel rearrangement.

References and notes

1. Zelder, F.; Sonnay, M; Prieto, L., *ChemBioChem*., **2015**, *16*, 1264-1278.
2. Lyden, P.; Pereira, B.; Chen, B.; Zhao, L.; Lamb, J.; Lei, L. F.; Rajput, P., *Stroke*, **2014**, *45*, 896-899.
3. Chinthakindi, P. K.; Naicker, T.; Thota, N.; Govender, T; Kruger, H.; Arvidsson, P. L., *Angew. Int. Ed. Engl.*, **2017**, *56*, 4100-4109.
4. Kocienski, P. J., *Protecting Groups 3rd edition*, Thieme: Stuttgart, **2000**.

5. Rushwinga, E.; Touray, H. K.; Bowen, R. D.; Gallagher, R. T.; Martin, W. H. C., *Tetrahedron Lett*., **2013**, *54*, 4726-4728.
6. Saidykhan, A; Bowen, R. D.; Gallagher, R. T.; Martin, W. H. C., *Tetrahedron Lett*., **2015**, *56*, 66-*68*.
7. Hara, O.; Hamada, Y., *Tetrahedron Lett.*, **1998**, *39*, 5537-5540.
8. Court, J. J.; Hlasta, D. J.; *Tetrahedron Lett*., 1996, 37, 1335-1338.
9. Watanabe, H.; Gay, R.; Hauser, C. R., *J. Org. Chem.*, **1968**, *33*, 900-903.
10. Lombardino, J. G., *J. Org. Chem*., **1971**, *36*, 1843-1845.
11. El Hiti, G. A.; Smith, K.; Hegazy, A. S.; Alshammari, M. B.; Masmali, A. H., *ARKIVOC*, **2015**, 19-47
12. Ould Aliyenne, A.; Khiari, J. E.; Kraiem, J.; Kacem, Y.; Hassine, B. B., *Tetrahedron Lett*., **2006**, *47*, 6405-6408.
13. Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D., *J. Med. Chem*., **1992**, *35*, 4613-4627.
14. Narasimhan, N. S.; Mali, R. S., *Synthesis*, **1983**, 957-986.
15. Clayden, J; Frampton, C. S.; McCarthy, C.; Westlund, N., *Tetrahedron*, **1999**, *55*, 14161-14184.
16. Parker, K. A.; Koziski, K. A., *J. Org. Chem.*, **1987**, *55*, 674-676.
17. Clayden, J.; Pink, J. H.; Yasin, S. A., *Tetrahedron Lett.*, **1998**, *39*, 105-108.

Supplementary Material

Illustrative experimental procedures and full experimental data for new compounds are provided.

Highlights

- The rearrangement can tolerate acidic protons.
- In sterically demanding substrates the saccharine is formed directly.
- The rearrangement of naphthalene derivatives is regioselective.