Tetrahedron Letters 53 (2012) 41–44

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A selective, tin-free radical mediated synthesis of indoles based on a sulfonate template

Vincent James Gray, Jonathan D. Wilden *

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

ARTICLE INFO

Article history:
Received 5 September 2011
Revised 30 September 2011
Accepted 17 October 2011
Available online 23 October 2011

Keywords:
Sulfonate ester
Indole
Radical
Cyclisation

ABSTRACT

A synthesis of indoles based on a vinyl sulfonate template is described. The approach employs a sulfonate group which plays three discrete roles in the synthetic sequence. Firstly the highly electron-withdrawing sulfonate group behaves as an activating group for a 1,4-addition of an aniline to the unsaturated system. Secondly, the electron-withdrawing nature of the same group also allows it to behave as a radical stabilising group which facilitates radical cyclisation to an aromatic ring to yield a transient indoline. Finally, the pendant sulfonate group behaves as a leaving group to yield the indole.

The chemistry and synthesis of indoles have long been of interest to the synthetic and medicinal chemist due to the varied biological and medicinal properties of these heterocycles.[1] Indoles are also extremely important pharmaceutical compounds finding a wide range of applications including 5HT-3 agonists,[2] non steroidal anti-inflammatory drugs (indomethacin and related compounds)[3] as well as numerous antibacterial agents.[4]

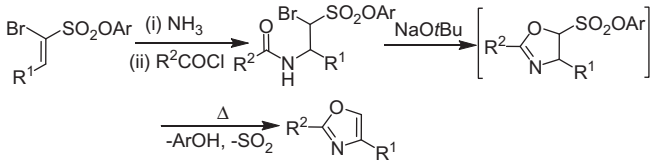
Synthetic approaches to indoles have largely relied on the manipulation of indole itself (particularly 3-substitution) or on the Fischer[5] or Bartoli[6] syntheses. As such, new and mild methods of forming these important ring structures are continually being sought.

We wondered if our previous efforts on the synthesis of heterocyclic compounds based on vinyl sulfonate or vinyl sulfonamide templates could be applied to the synthesis of indoles.[7] Our previous work has shown that a sulfonate template could be used to prepare heterocycles in a regiospecific manner (Scheme 1).

We were intrigued to know whether a radical addition to an aromatic ring would be a suitable strategy to construct the indole nucleus via a 1,4-addition of an aniline to the highly electron-deficient 1-bromo-2,4,6-trichlorophenyl (TCP) vinyl sulfonate **1**. This species is easily prepared from commercially available starting materials by the method of Aumaitre.[8] Our proposed strategy is outlined in Scheme 2 where the sulfonate group acts initially as an activating group, directing the 1,4-addition to the terminal carbon atom, then as a stabilising group for a radical generated by exposure to a non-tin based radical chain carrier such as EPHP (1-ethylpiperidine hypophosphite). Finally, on ring re-aromatisation the sulfonate moiety can act as a leaving group to install the overall aromaticity of the indole.[9]

We then set about establishing conditions to effect the 1,4-addition of an aniline to the vinyl sulfonate **1**. We were pleased to observe that the most efficient reaction occurred in the absence of solvent or any catalyst leading to the addition products **2a–j** in good yields for anilines bearing both electron-donating and electron-withdrawing groups. These observations highlight the extremely electron deficient nature of the vinyl sulfonate (Table 1).

Encouraged by the ease and efficiency of the 1,4-addition, we then turned our attention to the radical-mediated cyclisation reaction. Our first efforts in this respect proved to be unsuccessful. Exposing aniline **2a** to either phosphorus (EPHP) or tin (Bu_3SnH) based radical chain carriers did not yield any of the cyclisation products. Interestingly however, the starting aniline and debrominated vinyl sulfonate species **3** were isolated suggesting that the radical was generated but rather than cyclisation, elimination of aniline occurred to yield the observed products (Scheme 3).



Scheme 1. Synthesis of oxazoles based on a sulfonate template.

* Corresponding author.
E-mail address: j.wilden@ucl.ac.uk (J.D. Wilden).

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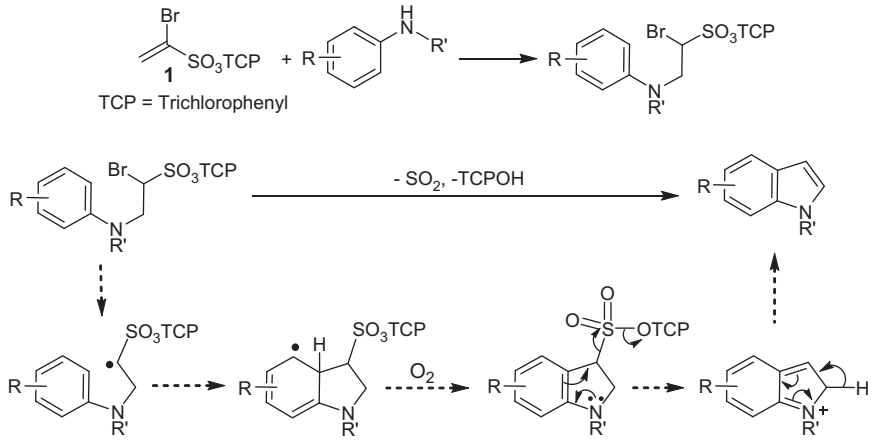
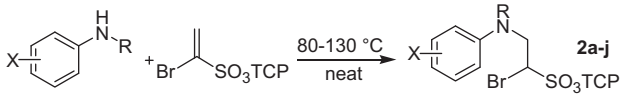
doi:10.1016/j.tetlet.2011.10.093

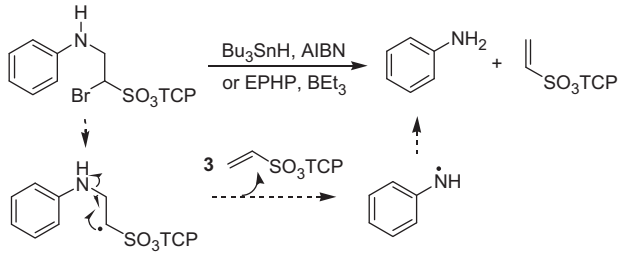


Scheme 2. Proposed strategy and mechanism for construction of indoles.

Table 1
Solvent-free 1,4-addition of anilines to 1-bromo-2,4,6-trichlorophenyl vinylsulfonate



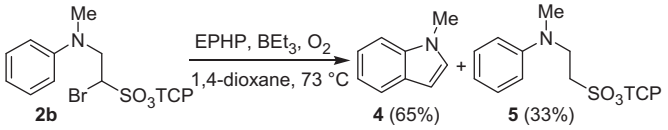
Entry	X	R	Product	Isolated yield (%)
1	H	H	**2a**	87
2	H	Me	**2b**	89
3	*p*-F	H	**2c**	92
4	*p*-Cl	H	**2d**	71
5	*p*-Br	H	**2e**	74
6	*p*-I	H	**2f**	78
7	*o*-OMe	H	**2g**	78
8	*m*-OMe	H	**2h**	65
9	*p*-SO_2NEt_2	Me	**2i**	14
10	*p*-CO_2Me	Me	**2j**	70



Scheme 3. Suggested mechanism for the elimination of aniline under free-radical conditions.

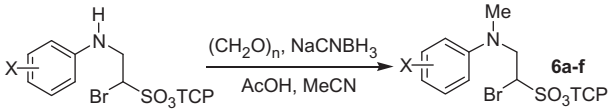
A survey of the literature revealed that radical reactions are seldom successful in the presence of free N–H bonds. With this in mind we reasoned that alkylation of the nitrogen atom would lead to a more efficient cyclisation and prevent the elimination of vinyl sulfonate ester **3**. Pleasingly, when **2b** was employed in the cyclisation reaction in air, indole **4** was isolated in reasonable yield along with a smaller amount of the reduced product **5** (Scheme 4).

Having established the necessity for nitrogen substitution, we set about methylating those 1,4-addition products with a free N–H bond in order to maximise the efficiency of the radical reactions. We found that in most cases the Corey modification[10] of the Eschweiler–Clarke reaction[11] gave good results (Table 2). Where this reaction fails (mainly for anilines bearing strongly electron-withdrawing groups) simple base-mediated methylation of aniline with methyl iodide could be effected prior to 1,4-addition.



Scheme 4. Radical mediated cyclisation and oxidation to yield N-methylindole.

Table 2
Corey modification of the Eschweiler–Clarke reaction to yield N-methyl anilines



Entry	X	Product	Isolated yield (%)
1	*p*-F	**6a**	73
2	*p*-Cl	**6b**	81
3	*p*-Br	**6c**	56
4	*p*-I	**6d**	46
5	*o*-OMe	**6e**	75
6	*m*-OMe	**6f**	71

Pleasingly, exposure of the methylated species to EPHP and triethylborane in air led to cyclised products in all cases with lesser amounts of non-cyclised reduced products. Standard EPHP radical conditions were employed,[12] however we found that maintaining the temperature of the reaction between 73 and 75 °C was critical for obtaining maximum yields of cyclised products. Temperatures below 73 °C resulted in the recovery of starting materials with a small amount of reduced product. Temperatures above 75 °C led almost exclusively to the uncyclised debrominated products **8a–i**. Although the yields were lower in some cases, (particularly where mesomerically electron-withdrawing substituents are attached to the aromatic ring) we were pleased to observe that the reaction was essentially quantitative with respect to the two products formed (Table 3, entries 1–7). No associated polymeric or unidentifiable material was produced and this reflects the ease of work-up and purification of EPHP as an alternative to tributyltin hydride. We also attempted the cyclisation with the α-iodide but found no advantage over using bromide. Our results are outlined in Table 3.

Perhaps most notable are entries 3–5 where the halogen atom (particularly the aryl iodide in entry 5) attached to the aromatic ring is untouched by EPHP, however the α-radical is readily formed. This example of selectivity is rare in radical chemistry