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Imination of sulfoxides using 3-acetoxyaminoquinazolinone as nitrogen source in the presence of hexamethyldisilazane

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Dedicated to Dr. R. S. Atkinson on the occasion of his 65th birthday

Abstract—The reaction of 3-acetoxyaminoquinazolinone (QNHOAc) with various sulfoxides in the presence of HMDS as an acetic acid scavenger, afforded the corresponding sulfoximides in good yields. Sulfoximidation of phenyl methyl sulfoxide using a Q*NHOAc having a stereogenic centre on its 2-position gave the products in 1.3:1 ratio of diastereomers.

The discovery of sulfoximides dates back to the late 1940s and early 1950s.[1] Since then, significant attention has been given to sulfoximides by synthetic organic chemists. Due to stereogenicity at the sulfur atom, sulfoximides have been used in pseudopeptides,[2,3] amino acids and amino alcohols[4] as well as in C–C bond formation.[5–8] Recently, Bolm,[9,10] Reggelin[1] and Tye[11] and their respective co-workers independently introduced sulfoximides as chiral ligands in asymmetric synthesis. A number of methods are known for the transformation of sulfoxides into sulfoximides using *tert*-butyloxycarbonyl azide ($BocN_3$),[12,13] *O*-mesitylenesulfonylhydroxylamine (MSH),[14,15] chloramine T[16,17] or [*N*-(*p*-tolylsulfinyl)imino]phenyliodinane (PhI = NTs)[18–21] or by an electrochemical process using *N*-aminophthalimide.[22,23] However, there is still a requirement for a general procedure for the conversion of sulfoxides into sulfoximides.

Aziridination of alkenes by lead tetraacetate (LTA) oxidations of 3-aminoquinazolinones **1** is a known method for the preparation of aziridines.[24] Where R is stereogenic centre, high,[25,26] or even completely[27] diastereoselective aziridinations (reagent-controlled) are obtained with moderate to good yields. We have recently reported that the substrate-controlled aziridinations of 8-phenylmenthol-derived α,β-unsaturated esters give aziridines completely diastereoselectively and the yields of these aziridines are greatly improved by the presence of hexamethyldisilazane (HMDS)[28,29] (Scheme 1). Additionally, a chiral 3-aminoquinazolinone **1** when converted into its 3-*N*,*N*-diacylaminoquinazolinone derivative **4**, is also an enantioselective acylating agent for racemic amines, for example **4a**, by means of kinetic resolution in up to 95% ee[30–32] (Scheme 1).

Although imination of dimethylsulfoxide (DMSO) by LTA oxidation of *N*-aminoheterocycles has been reported,[33] surprisingly, to the best of our knowledge, there are no reports on a general procedure for imination of sulfoxides using 3-amino-2-ethylquinazolinone **1** (R = ethyl) under the same conditions. Therefore, we report, herein, the first imination of sulfoxides using 3-acetoxyamino-2-ethylquinazolinone **2** (QNHOAc).

Initially, we examined the imination of DMSO with QNHOAc **2** and followed the general aziridination procedure (−18 °C to rt) using an equimolar quantity of DMSO. This reaction resulted in the desired sulfoximide

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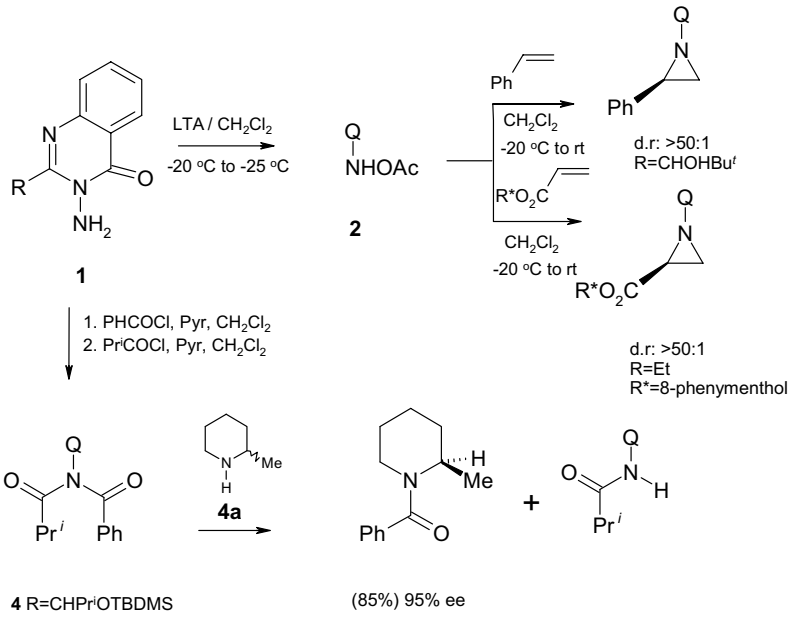
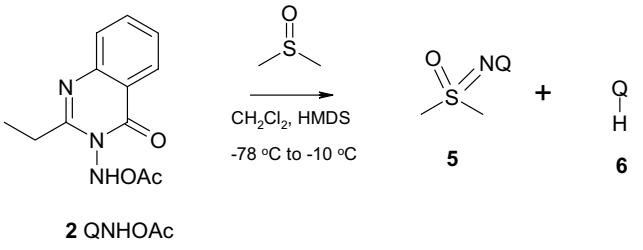
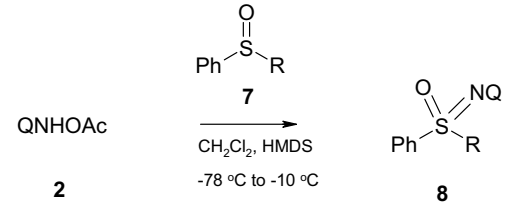


Scheme 1.



Scheme 2.



Scheme 3.

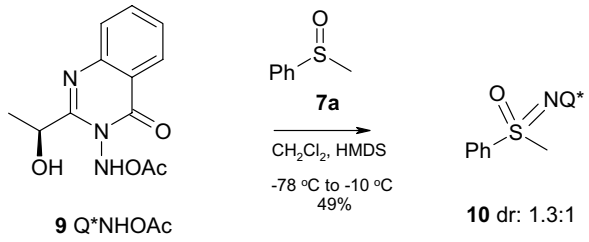
5 as a crystalline product (mp 130–132 °C) in 35% yield in addition to QH **6**, which is the general by-product of QNHOAc **2** aziridinations of alkenes, especially where electron deficiency is present[28,29] (Scheme 2). On increasing the molar equivalents of DMSO from 1 to 2 under the same conditions, the yield increased to 60%. Due to the instability of QNHOAc **2** (stable at <0 °C), we lowered the imination temperature to −78 °C and finished at −10 °C by adding a saturated $NaHCO_3$ solution, and extracting with CH_2Cl_2, to give an 80% yield. Experience from the aziridination process led us to use HMDS (2 equiv relative to QNH_2 **1**) to scavenge AcOH and this gave almost exclusively the sulfoximide **5** (95%) (Scheme 2).

We then turned our attention to the imination of phenylalkylsulfoxides **7a**–**f** using QNHOAc **2** under the optimised condition as described above. The sulfoximides **8a**–**f**[34] were obtained in good yields (Scheme 3). The ^1H NMR spectrum of the product from the imination of phenyl methyl sulfoxide with QNHOAc **2** showed that the methylene protons of the ethyl group in the products **8a**–**f** were diastereotopic as evidenced by a multiplet at 3.17 ppm. For example, the methylene protons of the ring ethyl in **8b** appeared at 3.17 and 3.51 ppm as two multiplets, respectively. Similarly, the methylene protons of the ethyl of the quinazolinone ring in **8f** resonated at 3.11 ppm as a multiplet, surprisingly, the other benzylic methylene protons appeared as a singlet at 4.71 ppm. All the sulfoximides **8a**–**f** were white crystalline materials (from ethanol) and had spectroscopic data as well as elemental analyses (±0.2) consistent with the sulfoximide structures (Table 1).

Table 1. Imination of phenylalkylsulfoxides (2 equiv) using QNHOAc **2** at −78 to −10 °C in the presence of HMDS

Entry	Sulfoxides	R	Products	Mp (°C)	Yield[a] (%)
1	**7a**	Me	**8a**	145–147	57
2	**7b**	Et	**8b**	155–157	61
3	**7c**	^{i}Pr	**8c**	119–121	61
4	**7d**	^{t}Bu	**8d**	127–128	60
5	**7e**	*c*-Hexyl	**8e**	136–138	62
6	**7f**	Bn	**8f**	161–163	70

The advantage of using 3-aminoquinazolinones in sulfoximidation, in particular, is the possibility of having a stereogenic centre at C-2, for example in Q*NHOAc **9**, which can give products diastereoselectively. A diastereoselective version of our procedure was carried out using lactic acid-derived Q*NHOAc **9**, and phenyl methyl sulfoxide giving sulfoximide **10** in 49% yield,



Scheme 4.

but, with virtually no diastereoselectivity (dr: 1.3:1) (Scheme 4).

In conclusion, we have developed a new method for the conversion of sulfoxides into sulfoximides using QNHOAc **2**. The yields were good in the presence of HMDS.

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34. Typical experimental procedure: 3-Amino-2-ethyl-quinazolinone QNH_2 **1** (0.3 g, 1.58 mmol) and acetic acid-free lead tetraacetate (LTA) (0.77 g, 1.75 mmol) were added alternately and continuously in very small portions over 15 min to a vigorously stirred solution of dry dichloromethane (6 cm^3) at −40 °C. The mixture was then stirred for a further 5 min to give a solution of the 3-acetoxyaminoquinazolinone. The temperature was lowered to −78 °C, before dropwise addition of the phenyl methyl sulfoxide (0.44 g, 3.17 mmol) as a solution in dichloromethane (3 cm^3) containing HMDS (0.51 g, 3.17 mmol) and then allowing the temperature of the solution to rise to −10 °C (~1.5–2 h) with continuous stirring. Saturated aqueous sodium hydrogen carbonate (30 cm^3) was added and the mixture extracted with dichloromethane (3×30 cm^3). The combined organics were washed with water (3×30 cm^3), dried with sodium sulfate and the solvent removed by evaporation under reduced pressure. The crude product crystallised on addition of ethanol to give sulfoximide **8a** as a colourless solid (0.3 g, 57%), mp 145–147 °C (from ethanol) IR (in CH_2Cl_2 solution) ν_{max} cm^{-1}: 3479w, 3011w, 2929w, 1675s, 1608w, 1591s and 1568w. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.35 (3H, t, J 7.3 Hz, CH_2CH_3), 3.17 (2H, m, CH_2CH_3), 3.31 (3H, s, $PhSCH_3$), 7.39–7.75 (m, 6-H, 7-H, 8-H (Q) and 3H (Ph)), 8.21 (1H, dd, J 8.2 and 1.1 Hz, 5-H (Q)) and 8.33 (2H, dd, 8.4 and 1.7 Hz, 2H (Ph)). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.8, 28.2, 43.8, 121.3, 126.2, 127.3, 128.8, 129.6, 134.1, 137.3, 146.8, 161.5 and 161.8). Elemental analysis calculated for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.13; H, 5.35; N, 12.97; S, 9.87.