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Novel Burgess reagent mediated C-to-N aryl migration reaction in nitrones[†]

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Nitrones undergo useful transformations with Burgess reagent. The reaction ostensibly involves a [3+2] annulation across a σ-bond followed by rearrangement involving C-to-N aryl migration. On the basis of available experimental evidence, plausible mechanisms for the rearrangement and the overall conversion have been proposed.

Burgess reagent (**1**) is a versatile reagent in organic synthesis[1,2] and its reactivity with a number of nucleophilic functional groups like alcohols, epoxides,[3,4] 1,2-diols,[5-8] thiols,[9,10] oximes[11] etc. are well documented. Newer applications[12-26] of the reagent as well as several modified forms of the reagent with improved thermal stability[11] are being reported. Now, chiral versions of the reagent are also known[26] enabling extensive use in organic natural product syntheses.

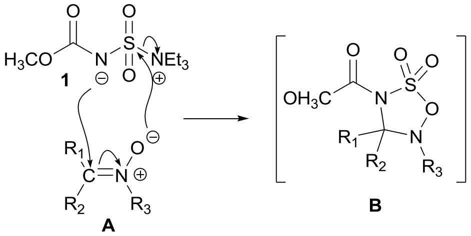

Figure 1

Burgess reagent (**1**) shows unexpected reactivity with *N*-oxides and the results are interesting and applicable in synthesis of several heterocyclic compounds, particularly those with pharmaceutical applications. A recent report shows an unexpected *N*-demethylation of oxymorphone and oxycodone-*N*-oxide using Burgess reagent to the corresponding oxazolidines providing a direct synthetic route to naltrexone, naloxone, and other antagonists from oxymorphone.[24] This report prompted us to investigate the reaction between nitrones and Burgess reagent. Nitrones being *N*-substituted 1,3-dipolar systems undergo [3+2] cycloaddition reactions with a variety of carbon–carbon, carbon–nitrogen, carbon–sulphur, nitrogen–phosphorus multiple bonded systems to give various heterocyclic systems.[27-33] Burgess reagent can be considered as a 1,2-dipole and hence can participate in a formal [3+2] annulation reaction with elimination of triethylamine with a complimentary 1,3-dipole to yield the corresponding five-membered heterocycle. Nitrones exhibit remarkable nucleophilicity[32,34] and hence are expected to react with Burgess reagent to give 1,2,3,5-oxathiadiazolidine intermediates **B** (Figure 1) in what may formally be regarded as a [3+2] annulation reaction across a σ-bond[31] (nitrogen-sulfur bond in this case).

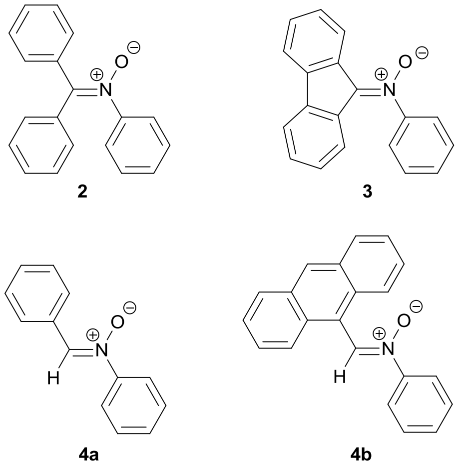

Figure 2

With a view to verify [3+2] annulation hypothesis and to exploit its synthetic potential, we examined the reaction of four structurally

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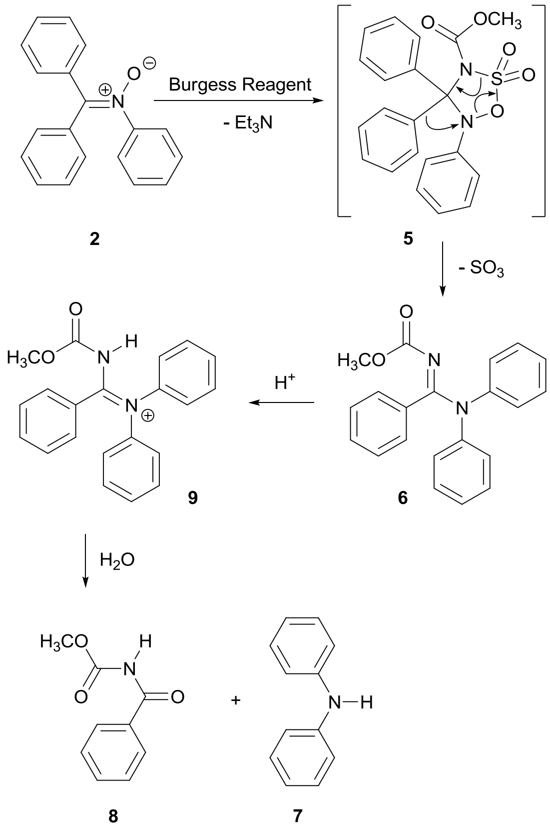
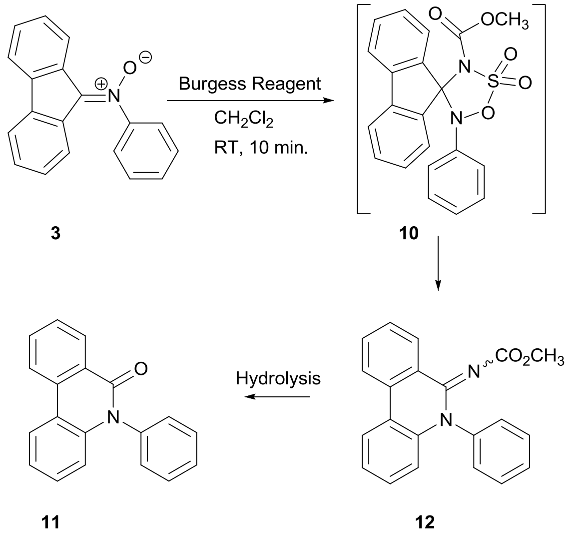
diverse nitrones[35-38] such as *N*-diphenylmethylene-*N*-pheylnitrone (**2**), *N*-fluorenylidene-*N*-pheylnitrone (**3**), (*Z*)-*N*-phenylmethylene-*N*-phenylnitrone (**4a**) and (*Z*)-*N*-(9-anthracenyl)methylene-*N*-phenylnitrone (**4b**) with Burgess reagent (Figure 2).

Reaction between *N*-diphenylmethylene-*N*-phenylnitrone (**2**) and Burgess reagent (**1**) was conducted in a 1:3 molar ratio in dry dichloromethane at room temperature. The product precipitated on adding hexane was identified as methyl (diphenylamino)(phenyl)methylenecarbamate (**6**, Scheme 1). In a repeat run, careful work up of the reaction mixture under absolutely moisture free conditions afforded, in addition to **6**, triethylamine-sulphur trioxde complex as colorless needles. Generation of **6** in the reaction between **2** and Burgess reagent mandates carbon to nitrogen aryl group migration. This rearrangement is reminiscent of a similar C-to-N aryl migration observed in the chlorosulfonyl isocyanate mediated transformation of nitrones[39,40] and Beckmann rearrangement of oximes. Though Burgess reagent is known to exhibit myriad reactivity, this is the first example for a C-to-N aryl migration promoted by this versatile reagent. Plausible mechanism for the C-to-N aryl migration reaction is provided in Scheme 1. Structure of carbamate **6** was further confirmed by chemical transformations. Acid hydrolysis of **6** gave diphenylamine (**7**) along with **8** in quantitative yields.



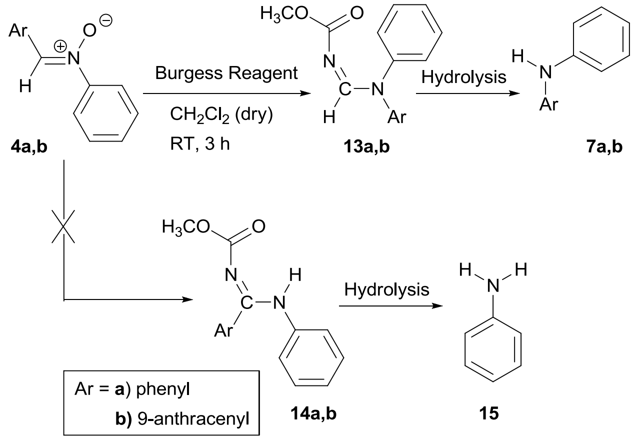
Scheme 1

In order to establish the generality of the novel C-to-N aryl migration observed by us, we examined the reaction of *N*-fluorenylidene-*N*-pheylnitrone (**3**) with Burgess reagent. In this case also, C-to-N aryl migration leading to ring expanded product **12** was observed. Carbmate **12** precipitated out on addition of dry hexane to the reaction mixture. It was separated, purified and characterized on the basis of spectral and analytical data and chemical transformations. Hydrolysis of **12** using dil. HCl gave 5-phenylphenanthridin-6(5*H*)-one (**11**) in high yields as the only isolable product.



Scheme 2

In continuation, we examined the reaction of (*Z*)-*N*-arylmethylene-*N*-phenylnitrones (**4a**,**b**) with Burgess reagent. In this case, the carbamate intermediates **13a**,**b** could not be isolated and the corresponding diarylamines **7a**,**b** were the only isolable products (Scheme 3). Though we could not isolate the carbmate intermediate **13a**,**b** generation of diarylamines **7a**,**b** is consistent with the C-to-N aryl migration pathway proposed by us. It may be noted that C-to-N hydrogen migration is an alternative possibility here. In order to check this possibility, we carried out careful GC-MS analysis of the reaction mixture. GC-MS analysis ruled out aniline generation in the reaction of **4a**,**b** with Burgess reagent and hence the alternative C-to-N hydrogen migration possibility.



Scheme 3

Conclusions

On the basis of the results obtained in the reaction of Burgess reagent with different nitrones, we demonstrated that the novel C-to-N aryl migration in the Burgess reagent–nitrone reaction is a general reaction as well. It appears that 1,2,3,5-oxathiadiazolidine intermediates generated through a [3+2] annulation pathway is a possible intermediate in the aryl migration reaction. Another striking feature of this rearrangement is the remarkable migratory aptitude observed here. In the case of **2** and **3**, migratory aptitude cannot be ascertained. However, with **4a**,**b** exclusive aryl group migration is observed. The migratory aptitude observed can be explained in two different ways: i) the more electron rich group migrates; ii) the *syn* group migrates. Mechanism of aryl group migration appears different from the one operating in Beckmann rearrangement.[41] Observed migratory aptitude is consistent with the involvement of a cyclic intermediate.[39,40] Detailed analysis of migratory aptitude is currently underway in our laboratory.

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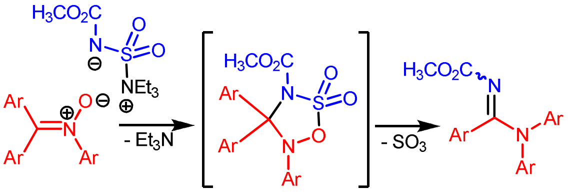
Graphical Abstract



Nitrones undergo useful transformations with Burgess reagent, ostensibly involving a [3+2] annulation across a σ-bond followed by rearrangement involving C-to-N aryl migration.

Key words: Burgess reagent, nitrones, [3+2] annulation, C-to-N aryl migration