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# A Mitsunobu reaction to functionalized cyclic and bicyclic *N*-arylamines

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ABSTRACT

The scope of an unexpected Mitsunobu cyclisation to prepare *N*-arylated *Fsp*$^3$-enriched azacycles was investigated. In the current study, we have identified whether a *p*Ka-dependent Mitsunobu cyclodehydration or a *p*Ka-independent Mitsunobu *intra*molecular reaction was in operation. A Mitsunobu reaction, creating a leaving group, followed by *intra*molecular nucleophilic displacement was determined to be the dominant pathway.



The Mitsunobu cyclodehydration reaction[1] is defined as the formation of azacycles from α,ω-aminoalcohols *via* a phosphonium intermediate. Due to mild reaction conditions and stereoinversion at the reacting centre, the Mitsunobu reaction has found widespread use.[2] The Mitsunobu cyclodehydration approach has found specialist uses, although less widespread application,[3] due to a variety of alternative methods to access azacycles.[4] These include acid catalysed dehydration, functionalisation of the alcohol to an appropriate leaving group, and the Appel reaction amongst others. An elegant application of the Mitsunobu cyclodehydration reaction has been reported by Park and co-workers[5] to access *trans*-2,3-disubstituted indolines from *N*-pivaloyl-2-aminophenethyl alcohols (Fig. 1). The reported mechanism abides by the *p*Ka rule for the Mitsunobu reaction (*p*Ka < 15 for the nucleophilic component)[6] with the *p*Ka of the anilide *N*H calculated[7] as *ca.* 14, and whereby the bulky electron withdrawing pivaloyl group is a pre-requisite for the reaction to occur.

During the course of our research programme, we encountered Mitsunobu cyclisation reactions occurring in examples where the calculated *p*Ka of the *N*H group was significantly greater than 15; e.g. for **1** (calculated *p*Ka 18.8) (Scheme 1).[8]

As shown in Scheme 1, we recently reassigned[8] the structure of a cyclin-dependent kinase (CDK) inhibitor as an alternative

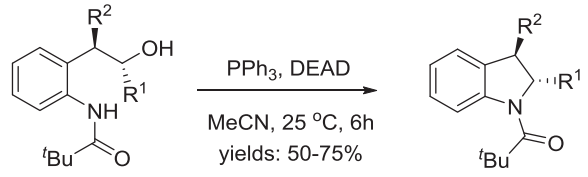
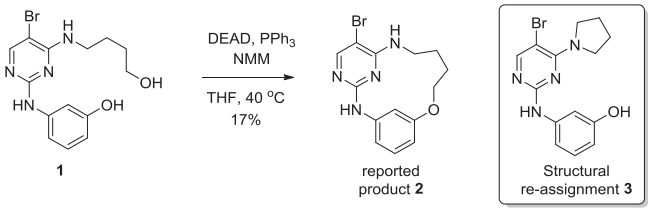



**Fig. 1.** The Mitsunobu cyclodehydration reaction reported by Park and co-workers.[5]




**Scheme 1.** Previous work[8] involving structural reassignment of the Mitsunobu products resulting from macroetherification.

Mitsunobu product to the proposed macrocyclic ether, that occurred *via* a Mitsunobu cyclodehydration. Most likely, the phenolic hydroxyl group in **1** acted as an initiating group for the Mitsunobu reaction to deliver **3** over the expected **2**.

In an unrelated medicinal chemistry program and the focus of this paper, we again unexpectedly observed the occurrence of a

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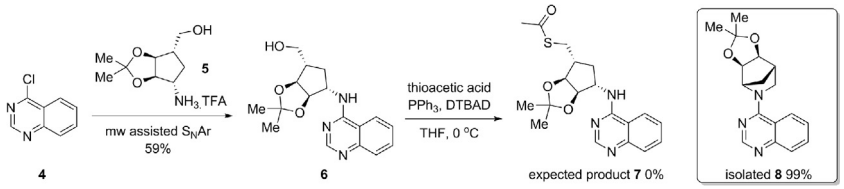



**Scheme 2.** An unexpected Mitsunobu cyclodehydration reaction afforded **8** over the expected **7**.

Mitsunobu cyclisation reaction affording the novel structure **8** (Scheme 2).[9]

The routine conversion of the 5′-alcohol of carbosugar **6**, prepared *via* microwave assisted $S_NAr$ of **4** and **5**, to a thioacetate group (using thioacetic acid, measured *p*Ka 3.3)[10] under standard Mitsunobu conditions did not afford the expected product **7**. Instead a novel product resulting from the *N*H group (calculated *p*Ka 17.6)[7] *intra*molecularly cyclising onto, the presumably, activated 5′-alcohol was isolated in quantitative yield (99%). Representative nOe correlations that demonstrate the 3D structure and connectivity of **8** are shown in Fig. 2.[11]

Prompted by these results and other examples of both Mitsunobu cyclisation and cyclodehydration reactions,[12] as well as the Mitsunobu *p*Ka rule[13] we considered several factors as to why **8** was formed in preference to **7**:

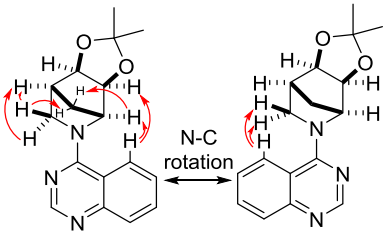
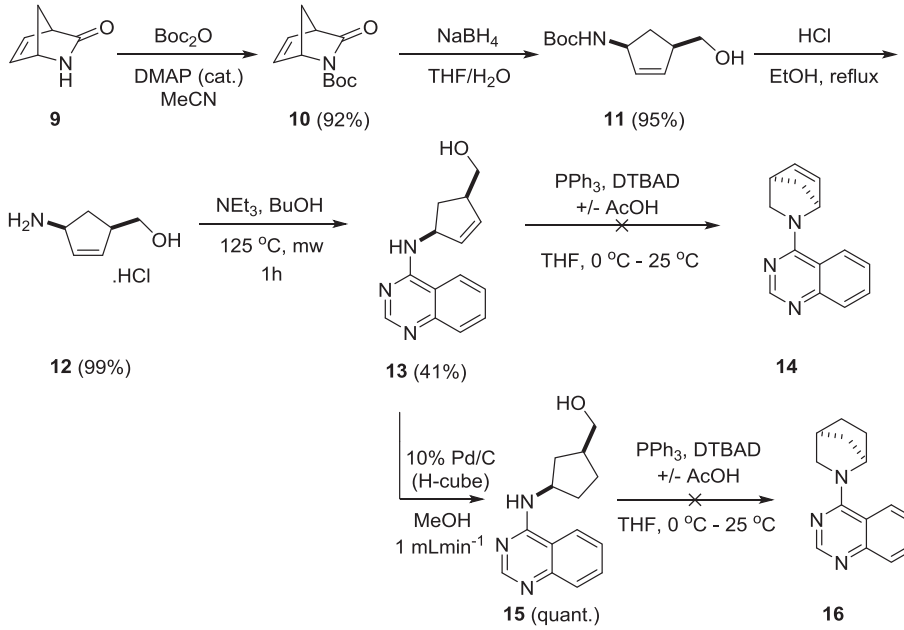



**Fig. 2.** Selected nuclear Overhauser exchange (nOe) correlations detected in the NMR spectrum of **8** that demonstrate the new C-N connectivity resulting from Mitsunobu cyclodehydration.[11]

- Is a thio-Mitsunobu reagent formed?
- Is there a steric requirement to cyclisation?
- Can the *p*Ka rule be extended?

These observations are addressed in the following sections. The presence of both triphenylphosphine oxide and triphenylphosphine thioxide were detected by mass spectrometry of the crude reaction mixture from the conversion of **6** → **8** (Scheme 2). The reaction was repeated under identical conditions with the replacement of thioacetic acid by acetic acid to probe if a thio-Mitsunobu mechanism was operating. Under analogous conditions with acetic acid, **8** was again isolated exclusively, thus ruling out this pathway. The observation of $PPh_3$ = S, presumably from the reaction of triphenylphosphine with thioacetic acid[14] was therefore shown to be not involved in the reaction pathway of **6** → **8** (Scheme 2).

To probe whether steric compression in **6** caused by the acetal protected diol (between the *N*-orbital of the quinazoline and the hydroxyl leaving group) was the cause or enhanced the rate of cyclisation of **6** → **8**, two control compounds **13** and **15** were synthesised without the dihydroxy sugar motif (Scheme 3). Molecular modelling (using MM2 calculations) showed **13** and **15** to have comparable distances between the reacting *N*H and *O*H centres as in **6** (3.7 Å (**15**) – 4.8 Å (**13**) *vs.* 5.0 Å (**6**), respectively).[15] The preparation of **13** began with di-*tert*-butyldicarbonate protection of vince lactam **9** to afford **10** in excellent yield. Sodium borohydride mediated reductive ring cleavage of **10** afforded the ring-opened product, **11**.[16,17] Acid mediated deprotection of **11** proved facile yielding **12** as the hydrochloride salt. Subjection of a mixture of 4-chloroquinazoline and **12** to microwave assisted $S_NAr$




**Scheme 3.** Preparation of model compounds **13** and **15** for attempted Mitsunobu cyclisations.