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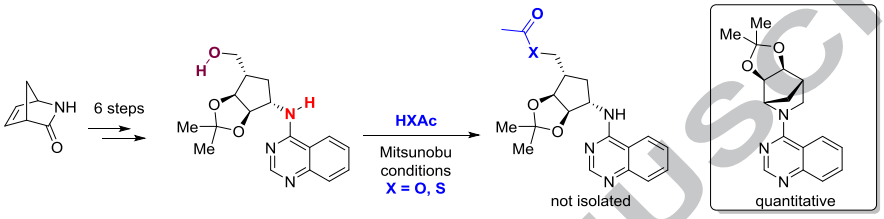
Daniel M. Gill,[ab] Matthew Iveson[c], Ian Collins[d], Alan M. Jones[a]*



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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 *F*sp^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 the 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] including 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.

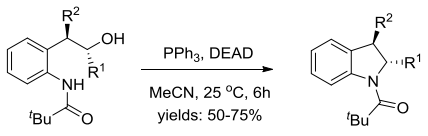
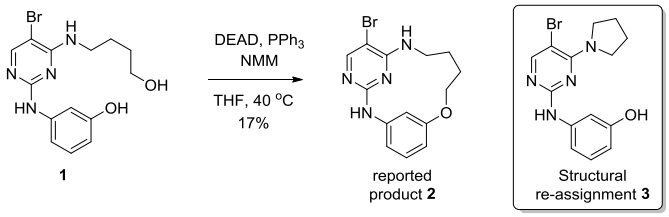


Figure 1. The Mitsunobu cyclodehydration reaction reported by Park and co-workers.[5]

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]



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

As shown in Scheme 1, we recently reassigned[8] the structure of a cyclin-dependent kinase (CDK) inhibitor as an alternative 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 Mitsunobu cyclisation reaction affording the novel structure **8** (Scheme 2).[9]

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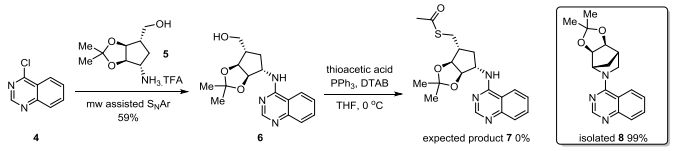


Scheme 2. An unexpected Mitsunobu cyclodehydration reaction afforded **8** over the expected **7**.

The routine conversion of the 5'-alcohol of a 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] 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 Figure 2.[11]

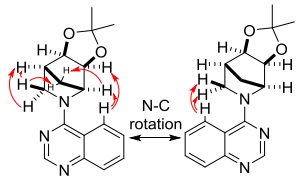


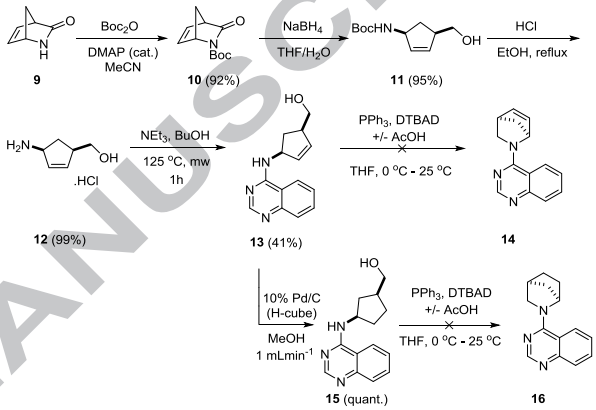
Figure 2. Selected nuclear Overhauser exchange (nOe) correlations detected in the NMR spectrum of **8** that demonstrate the new C-N connectivity resulting from Mitsunobu cyclodehydration.[11]

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**:

- 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** to **8** (Scheme 2A). 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** to **8** (Scheme 2A).

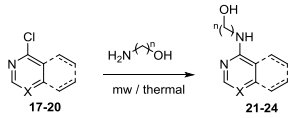
To probe whether steric compression in **6** caused by the acetal protected diol (between the *N*-orbital of the quinazoline and the hydroxyl leaving group) was the cause or enhanced the rate of cyclisation of **6** to **8**, two control compounds **13** and **15** were synthesised without the dihydroxy 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 conditions afforded **13** in modest yield. It was found that subjection of **13** to the standard Mitsunobu cyclodehydration reaction conditions of triphenylphosphine and di-*tert*-butylazodicarboxylate (DTBAD) did not afford **14** either with or without acetic acid. Instead, recovered starting material and decomposition products resulted. This outcome suggested that steric compression from the 2',3' protected alcohols played a significant factor in the high yielding formation of **8** (Scheme 2) possibly due to a *pseudo*-Thorpe Ingold rate acceleration.[17] To further probe the difference between **6** containing an sp^3-sp^3 bridge and **13** containing an sp^2-sp^2 bridge, compound **13** was reduced to afford **15**. When subjected to standard Mitsunobu conditions, **15** did not afford a cyclised product, supporting the assertion that the original architecture of **6** enhanced the formation of Mitsunobu cyclisation product **8** over Mitsunobu substitution product **7**.



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

*p*Ka and ring size effects in model systems

It became apparent that steric compression played a factor in the formation of **8**, enabling the amino and 5'-hydroxyl groups to be in close proximity. However, the question of whether this Mitsunobu cyclodehydration reaction would be possible in simpler and potentially more often encountered systems remained to be studied. Therefore, a simplified system probing the *p*Ka of the secondary amine *N*H of the aryl amino group and its effect on Mitsunobu cyclisation was investigated. Examples of the reaction precursors prepared are shown in Table 1.



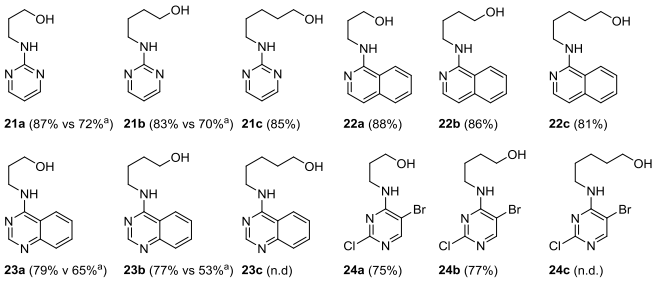
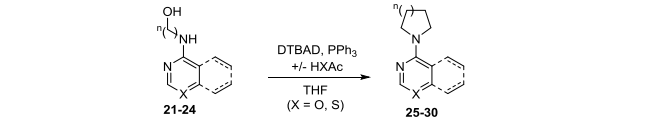
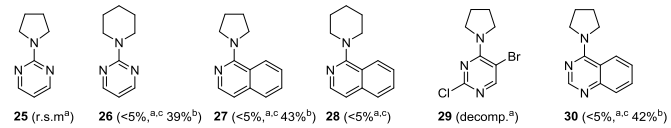


Table 1. Preparation of model S_NAr products. Isolated yield from microwave irradiation reported in brackets. [a]Comparative yield for thermal S_NAr conditions; n.d. not determined. Reagents and conditions: heteroaryl chloride (1.0 eq.), aminoalcohol (1.1 eq.), NEt_3 (1.5 eq.) and *n*-BuOH (1 mL) were either irradiated at 125 °C (30 W) in a microwave reactor for 1 h or heated at reflux for 16 h.

The S_NAr reaction (Table 1) proved robust with 10 high yielding reaction products from 12 reactions, with no discernible difference in yield based on the carbon chain length of the aminoalcohol. In two cases, **23c** and **24c**, the aminopentanol reaction gave a complex mixture which prevented isolation (compared with **21c** and **22c**, respectively). This may be due to competitive *N*- and *O*- nucleophilic substitution when a less reactive electrophile is employed.

Four direct comparisons of microwave irradiation and traditional thermal heating were examined, **21a-b** and **23a-b**. In all cases microwave irradiation proved superior, delivering higher conversions and subsequently, isolated yields of the S_NAr products. All successful S_NAr products were subjected to the standard Mitsunobu conditions (Table 2).





25 (r.s.m.[a]) *p*Ka = 16 | **26** (<5%,[a,c] 39%[b]) *p*Ka = 16 | **27** (<5%,[a,c] 43%[b]) *p*Ka = 22 | **28** (<5%[a,c]) *p*Ka = 22 | **29** (decomp.[a]) *p*Ka = 19 | **30** (<5%,[a,c] 42%[b]) *p*Ka = 20

Table 2. Transformation of selected examples of **21-24** to azacycles **25-30**. [a]without AcOH; [b]addition of AcOH (1.0 equiv.); [c] addition of AcSH (1.0 equiv.). Reagents and conditions: aminoalcohol (1.0 eq.), (thio)acetic acid (1.0 eq.), PPh_3 (1.5 eq.), DTBAD (1.5 eq.) and THF (5 mL) was stirred at 0 ^oC to 25 ^oC for 24-48 h.

Table 2 demonstrates that in examples where the *p*Ka of the *N*H group is greater than 15 (calculated *p*Ka range 16-22), only trace yields of the cyclised product formed when a more acidic proton donor (AcOH) was not present. In selected examples where an additional proton donor is present (1.0 equiv. of acetic acid), reactions that previously did not deliver the azacycle proceeded in modest yield. Most likely, in these examples an acetate leaving group was installed *via* a classic Mitsunobu reaction followed by cyclisation.[18] Evidence for the acetate leaving group formation was identified in the crude ^1H NMR spectra. This is also a plausible mechanism by which **8** formed from **6** in Scheme 2A, *via* a (thio)acetate leaving group. However, the use of a stronger acid source, thioacetic acid, proved counterproductive in examples **26-28** and **30**. All examples of the aminopropanol containing compounds failed to deliver the corresponding 4-membered azacycles (not shown), which could be attributed to the ring strain that would result. The fact that a trace reaction occurred in selected reactions (without an additional proton donor), suggests it may be a possible for the competing Mitsunobu cyclodehydration to operate but may also be due to adventitious water initiating the reaction giving rise to the capricious nature of these reactions when the *p*Ka of the *N*H group is greater than 15. In all the successful examples of the cyclisation, it was found that heating the reaction, to try to force the reaction to completion, reduced the yield of the product. Importantly, the successful reactions in Table 2 demonstrate that an *intra*molecular hydrogen bond between the 5'-OH group and one of the oxygens of the acetal in **6** that could possibly activate the alcohol in the Mitsunobu reaction to **8** was not essential for reactivity.

Finally, to probe whether a non-competent mineral acid (eg. HCl) could be used to activate the azodicarboxylate compound to form the betaine Mitsunobu intermediate (but not form a leaving group) was attempted. Syringe-pump addition of 4.0 M HCl in dioxane to reaction mixtures without a competent acid group (based on calculated *p*Ka) failed to deliver the cyclised products **26**, **27** and **30**. This information, combined with the previous experiments suggests in the original example (**6** → **8**)[19] the *p*Ka effect of the *N*H group is not as important as the formation of a leaving group on the hydroxyl group and therefore **8** was most likely formed *via* a Mitsunobu cyclisation instead of a cyclodehydration reaction. Our results suggest the Mitsunobu *p*Ka argument holds.

Herein, we report a complex example of an unexpected Mitsunobu cyclisation reaction. The mode of reaction, steric parameters and *p*Ka effects that induced this reaction were investigated, revealing the steric compression required for 5'-activation in the carbosugar. Furthermore, we investigated a range of potential ring sizes that could be accessed *via* Mitsunobu cyclisation in a series of 10 aryl aminoalcohols prepared *via* S_NAr chemistry. It is of importance to note that when the *N*H group is insufficiently acidic to initiate a cyclodehydration reaction, an additional Mitsunobu-competent acid can rescue the reaction. In this case a traditional Mitsunobu intramolecular reaction creating a leaving group, followed by an intramolecular displacement that no longer involves the Mitsunobu reagents occurs, but remains dependent on the nucleophilicity of the *N*H group.

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References and notes

1. For recent reviews of the Mitsunobu and cyclodehydration reactions see: (a) Fletcher, S. *Org. Chem. Front.* **2015**, *2*, 739-752; (b) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340-1355.
2. Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551-2651.
3. (a) Wang, F.; Hauske, J. R. *Tetrahedron Lett.* **1997**, *38*, 6529-6532; (b) Whiting, E.; Lanning, M. E.; Scheenstra, J. A.; Fletcher, S. *J. Org. Chem.* **2015**, *80*, 1229-1234; (c) Garcia-Delgado, N.; Riera, A.; Verdaguer, X. *Org. Lett.* **2007**, *9*, 635-638.
4. (a) Wang, Y.; Oriez, R.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K.-I. *J. Org. Chem.* **2016**, *81*, 2652-2664; (b) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P.; Schofield, T. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 9223-9235
5. Kang, K. H.; Kim, Y.; Im, C.; Park, Y. S. *Tetrahedron* **2013**, *69*, 2542-2549.
6. For *p*Ka effects in the Mitsunobu reaction see: (a) Mitsunobu, O. *Synthesis*, **1981**, *1*, 2; (b) Huges, D. L. *Organic Reactions*, **1992**, *42*, 335 (John Wiley & Sons, Inc., New York); (c) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *13*, 1279.
7. ACE & JChem® pKa calculator, available at: https://epoch.uky.edu/ace/public/pKa.jsp
8. Jones, A. M. *Molbank* **2015**, M859.
9. (a) Cheeseman, M. D.; Westwood, I. M.; Barbeau, O.; Rowlands, M.; Dobson, S.; Jones, A. M.; Jeganathan, F.; Burke, R.; Kadi, N.; Workman, P.; Collins, I.; van Montfort, R. L. M.; Jones, K. *J. Med. Chem.* **2016**, *59*, 4625−4636; (b) Jones, A. M., Westwood, I. M., Osborne, J. D., Matthews, T. P., Cheeseman, M. D., Rowlands, M. G., Jeganathan, F., Burke, R., Lee, D., Kadi, N., Liu, M., Richards, M.; McAndrew, C., Yahya, N., Dobson, S. E., Jones, K., Workman, P., Collins, I., van Montfort, R. L. M. *Sci. Rep.* **2016**, *6*, 34701.
10. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.
11. See ESI.

12. Selected examples of Mitsunobu macrocyclisation: (a) Lucking, U.; Siemeister, G.; Schafer, M.; Briem, H.; Kruger, M.; Lienau, P.; Jautelat, R. *ChemMedChem* **2007**, *2*, 63-77; (b) Arasappan, A.; Chen, K. X.; Njoroge, C. F. G.; Parekh, T. N.; Girijavallabhan, V. *J. Org. Chem.* **2002**, *67*, 3923-3926; (c) Chen, K. X.; Njoroge, F. G.; Pichardo, J.; Prongay, A.; Butkiewicz, N.; Yao, N.; Madison, V.; Girijavallabhan, V. *J. Med. Chem.* **2006**, *49*, 567-574.
13. For references to the *p*Ka rule see: (a) Mitsunobu, O. *Synthesis* **1981**, 1-28; (b) Huges, D. L. The Mitsunobu Reaction "Organic Reactions" Vol. 42, eds, by P. Beak, *et al*., John Wiley & Sons, Inc., New York, **1992**, 335; (c) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *13*, 1279-1282.
14. (a) Guzaev, A. P. *Tetrahedron Lett.* **2011**, *52*, 434-437; (b) Sugimoto, H.; Tatemoto, S.; Toyota, K.; Ashikari, K.; Kubo, M.; Ogura, T.; Itoh, S. *Chem. Commun.* **2013**, *49*, 4358-4360; (c) Tran, C. T.; Williard, P. G.; Kim, E. *J. Am. Chem. Soc.* **2014**, *236*, 11874-11877; (d) Attanasi, O. A.; Bartoccini, S.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *J. Org. Chem.* **2012**, *77*, 9338-9343.
15. See ESI for molecular modelling comparisons.
16. Kudoh, T.; Fukuoka, M.; Ichikawa, S.; Murayama, T.; Ogawa, Y.; Hashii, M.; Higashida, H.; Kunerth, S.; Weber, K.; Guse, A. H.; Potter, B. V. L.; Matsuda, A.; Shuto, S. *J. Am. Chem. Soc.* **2005,** *127*, 8846.
17. Hensbergen, A. W., Mills, V. R., Collins, I., Jones, A. M. *Tetrahedron Lett.* **2015**, *56*, 6478-6483.
18. Chuchani, G.; Al-Awadi, N.; Dominguez, R. M.; Kaul, K. *J. Phys. Org. Chem.* **2001**, *14*, 180-186.
19. Typical procedure: (3a*R*,4*S*,7*S*,7a*S*)-2,2-Dimethyl-5-(quinazolin-4-yl)hexahydro-4,7-methano[1,3]dioxolo[4,5-*c*]pyridine (**8**). The heterocycle-substituted amino alcohol (1.0 eq.), thioacetic acid (1.0 eq.), triphenylphosphine (1.5 eq.) and di-*tert*-butyl azodicarboxylate (DTBAD) (1.5 eq.) were dissolved in anhydrous THF (5 mL) at 0 ^{o}C and allowed to gradually warm to 25 ^{o}C with stirring over 24 h. The reaction mixture was purified by gradient elution flash column chromatography (Ethyl acetate : petroleum ether; 25:75) to afford **8** as a clear oil (45 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.57 (s, 1H), 8.02 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 7.69 (dd, *J* = 7.0 Hz, 1.5 Hz, 1H), 7.38 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 4.94 (dd, *J* = 2.0, 1.0 Hz, 1H), 4.46 (dt, *J* =5.5, 1.5 Hz, 1H), 4.27 (dd, *J* = 5.5, 1.5 Hz, 1H), 3.98 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.24 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.11 (s, 1H), 2.74 (dd, *J* = 4.0, 2.0 Hz, 1H), 1.65 (dt, *J* = 10.5, 1.5 Hz, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.8, 154.5, 151.6, 133.1, 132.1, 128.7, 124.9, 116.0, 110.5, 80.2, 79.1, 60.9, 51.4, 40.6, 30.5, 25.6, 24.3; LCMS (100% AUC) ESI: *m/z* 298 $[M+H]^+$; HRMS calcd. 298.1556 ($C_{17}H_{20}N_3O_2$, $[M+H]^+$); found 298.1533.

Supplementary Material

Characterisation and experimental details of novel and known compounds and ^{1}H, ^{13}C NMR spectra associated with this article can be found in the online version, at XXX

Highlights

- An unexpected Mitsunobu route to *N*-arylated azacycles
- Mitsunobu Cyclodehydration versus Intramolecular cyclisation investigated
- Reaction scope, ring size, steric and *p*Ka effects studied in model systems