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On the regiochemistry of Mitsunobu alkylations of hydrazine derivatives

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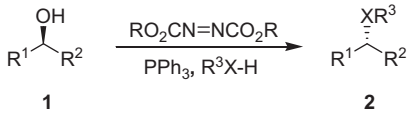
ABSTRACT

That differentially protected hydrazines of the type TsNHNHCOR^3 undergo regiospecific Mitsunobu reactions with a variety of alcohols, R^{1}R^{2}CHOH in a generalised manner, to give good to excellent yields of the mono-adducts Ts(R^{1}R^{2}CH)NNHCOR^3, has been proven by X-ray crystallographic analysis.

The Mitsunobu reaction (Scheme 1) is of crucial importance for the introduction of a variety of heteroatomic species, including oxygen-, nitrogen- and sulfur-based species and even some nucleophilic carbon reagents by displacement of, overall, the hydroxyl group in a precursor alcohol **1**.[1] Proceeding by an exquisitely controlled S_N2 inversion mechanism in the last step, perhaps its only significant drawback is the sometimes Herculean efforts required to separate the desired product **2** from the spent reagents, a phosphine oxide and a hydrazine dicarboxylate or relative, along with the necessary slight excesses of the initial reagents. Recently, even this feature has been addressed.[2]

Just prior to its discovery, during studies carried out in Mukaiyama's laboratory which doubtless led to this major advance,[3] what can be regarded as a 'halfway house' or partial version of the Mitsunobu reaction was logically developed wherein the final nucleophilic species, R^{3}XH, was omitted. As now the only reactive nucleophile is the 'spent' hydrazine, the overall reaction results in mono-*N*-alkylation of the latter; ironically, at the time of its discovery, there was more emphasis placed on the fact that this was a method for the oxidation of trivalent phosphorus compounds (Scheme 2).[4] For a separate study, we required a diverse series of such monoalkylated hydrazines and clearly this methodology could provide a small number of these, starting from the limited range of commercially available and symmetrical azodicarboxylates.

Mechanistically, this reaction presumably begins by nucleophilic addition of the phosphine to the azodicarboxylate to generate the same initial adduct **3** which is involved in the normal Mitsunobu reactions.[1] Subsequent addition of the precursor alcohol to this intermediate then leads to the penultimate species **4**, which can then reorganise, either intramolecularly or possibly via the highly activated intermediate **7**, to give the observed products—the alkylated hydrazine dicarboxylate **5** and the phosphine oxide **6**. It is interesting to note that this reaction does not interfere



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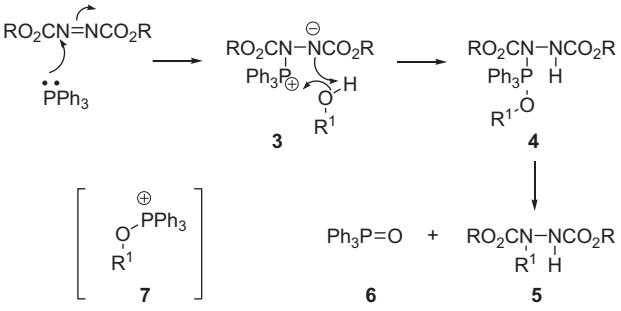
Scheme 1. A typical Mitsunobu reaction.



Scheme 2. Synthesis of a mono-*N*-alkyl-1,2-hydrazine dicarboxylate.

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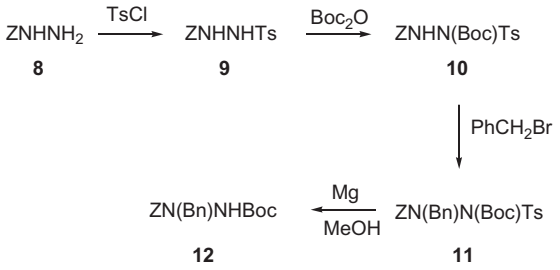
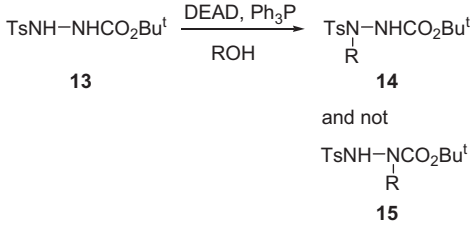


Scheme 3. A non-Mitsunobu approach to a mono-alkylated hydrazine dicarbox ylate.



Scheme 4. The Ragnarsson regiospecific alkylation of an unsymmetrical hydrazine.

to any appreciable extent in the Mitsunobu reaction itself.[1] It is also notable that double alkylation does not occur and that hydrazine-1,2-dicarboxylates are very poor substrates for Mitsunobu reactions in general, both of which observations support this intramolecular alkylation mechanism, rather than any involvement by the activated species **7**.

Later studies have established that a key rate determining step in the Mitsunobu reaction is breaking of the X–H bond in the incoming nucleophilic species. Hence, the pK_a value of such a nucleophile is a crucial determinant of its suitability, rather than its inherent nucleophilicity. This is well illustrated by the work of Martin and Dodge who showed that 4-nitrobenzoic acid is a far superior component of a Mitsunobu reaction than the parent benzoic acid.[5] This feature was later quantified by the Ragnarsson group, in seminal work which suggested an optimum value for such a pK_a of <13.5, for values determined in dimethyl sulfoxide.[6]

Subsequently, the same group returned to the original Mukaiyama methodology (Scheme 2) for hydrazine alkylation and provided more examples which attested to the importance of this relatively low pK_a value in the incoming nucleophile. Prior to this, a somewhat lengthier scheme was required to obtain a selectively mono-alkylated, unsymmetrical hydrazine-1,2-dicarboxylate **12** (Scheme 3).[7]

Thus, starting with a hydrazine mono-carboxylate **8**, sulfonation[8] of the free amino group gives the doubly protected species **9** which, in line with the following selective Mitsunobu method, then undergoes selective alkoxycarbonylation at the more acidic sulfonamide site to give the triply protected hydrazine derivative **10**. This then can only be alkylated at the remaining free position; subsequent detosylation of the resulting fully substituted hydrazine **11** finally yields the unsymmetrically protected mono-alkylated hydrazine-1,2-dicarboxylate **12**.

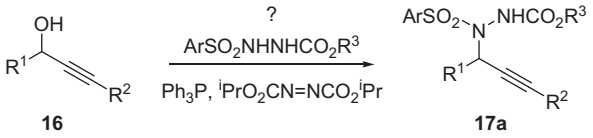
When recently we required a series of such mono-alkylated-1,2-hydrazine dicarboxylates, for example **12** and the related sulfonyl derivatives **14**, we were obviously attracted to the idea of using the direct mono-alkylation approach, but using an unsymmetrically protected hydrazine, rather than the method shown in Scheme 2, which is limited to the formation of symmetrical 1,2-dicarboxylates. We found that the Ragnarsson group had indeed reported two such examples in a later publication,[9] wherein it was stated that the unsymmetrical hydrazine derivative **13** underwent regiospecific alkylation at the sulfonamide function rather than at the alternative carbamate site to give excellent yields of the derivatives **14** [R = *p*-MeOC$_6$H$_4$CH$_2$ and Me$_2$CHCH$_2$] (Scheme 4).

The explanation, and indeed structural assignments as products **14** and not **15**, for these potentially very useful results were based entirely on considerations of pK_a values. Thus, as argued above, X–H bonds with lower values are more reactive in Mitsunobu and related reactions as breaking of this bond is a key rate determining step. Prior work by Bordwell had established a relative pK_a value of 22.2 for the N–H bond in carbamate derivatives, EtO_2C*NH*NH_2, while the corresponding value for similar sulfonamides, ArSO_2*NH*NH_2, was 17.1,[10] very much in agreement with the measurements reported subsequently by the Ragnarsson group.[6,8,9] The sole formation of the monoalkylated products **14** was therefore ascribed, not unreasonably, to this large difference, which predicts a product ratio of ca. 10,000:1, a difference which we presumed could be extrapolated to doubly protected hydrazine derivatives such as the sulfonamides **13**.

Despite these compelling arguments, the structural assignments were not supported by any other data beyond the apparent homogeneity of the single products obtained in the two examples reported. For at least two reasons, this seemed to us to be insufficient and indeed somewhat risky. Firstly, this type of hydrazine derivative typically produces very poorly resolved NMR spectra, even at elevated temperatures, due to extensive rotameric broadening. The ^{1}H NMR data reported for the products **14** (or **15**) consist of a series of broad resonances,[9] which also proved to be a serious problem in our own work and provided very little convincing evidence to distinguish the two possible products. The reported[9] presence of two separate conformers, as we also often observed, merely increased this uncertainty. Secondly, there is considerable mechanistic ambiguity associated with many details of the Mitsunobu reaction in general (See Ref. [1b,c] for an extensive discussion of this aspect). For example, it is not inconceivable that, while initial reaction occurs preferentially at the sulfonamide N–H group, during the later stages this could give rise to an unanticipated intermediate, which could react by subsequent transfer of the alkylating group to the other N–H group, by reason of its greater nucleophilicity (cf. Scheme 2). These two factors understandably also made us nervous about using alternative, multistep synthetic routes to provide structural proof.

The particular series of hydrazine derivatives that was required for a separate study,[11] was based on general formula **17a**, the optimum precursors being the corresponding alcohols **16** as these were readily available from condensations between acetylides and aldehydes (Scheme 5). In fact, the relative sensitivity of these secondary propargylic alcohols **16** made us wonder if the reaction would work at all, prior to any considerations regarding regioselectivity.

In the event, we found that the reaction proceeded slowly but very cleanly[12] and delivered an excellent yield of 91% of the first example [**17a**; R^1 = ^{i}Bu, R^2 = Bu, R^3 = ^{t}Bu, Ar = *p*-MeC_6H_4] of this reaction, quite clearly as a single product.[13] A considerable bonus was that the product was a crystalline solid, suitable for X-ray crystallographic analysis. The refined ORTEP diagram subsequently obtained is shown in Figure 1.[14]



Scheme 5. The desired Mitsunobu alkylation.

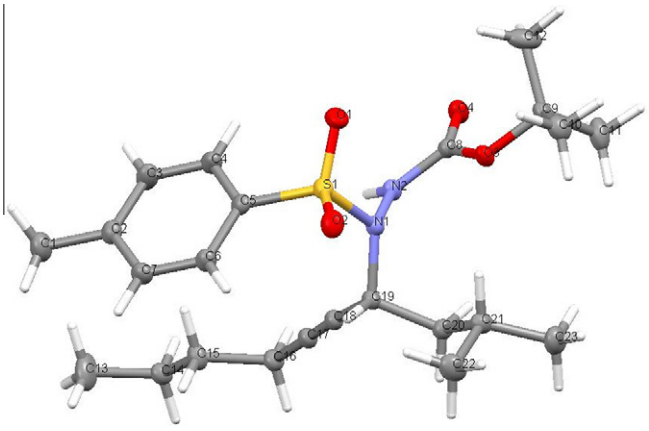
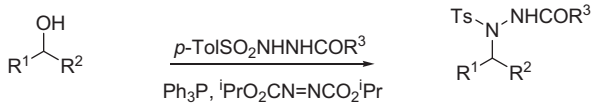
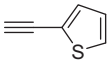
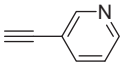
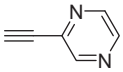
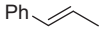
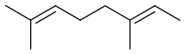


Figure 1. ORTEP diagram of the Mitsunobu adduct **17a** [R^1 = ^{i}Bu, R^2 = Bu, R^3 = ^{t}Bu, Ar = *p*-MeC_6H_4]. CCDC 783430.

Table 1
Mitsunobu reactions using *N*-tosyl-*N*′-carbonylhydrazines



18 **19**

Entry	R^1	R^2	R^3	Yield (%)
1	^{i}Bu	≡—Bu	O^{t}Bu	91 (= **17a**)
2	^{i}Bu	≡—Ph	O^{t}Bu	78 (= **17b**)
3	Me		O^{t}Bu	75
4	Me		O^{t}Bu	66
5	Me		O^{t}Bu	64
6	^{i}Bu	≡—Bu	Me	77
7	^{i}Bu	≡—Ph	Me	67
8		H	OMe	89
9		H	OMe	90
10		H	OMe	91
11	Bu	H	OMe	75

In just the same way, the related Mitsunobu product **17b** obtained from the corresponding phenyl substituted alcohol, derived from phenylacetylene and isovaleraldehyde, also gave excellent crystals for X-ray analysis. Once again, the only product was that arising from reaction at the NHTs function (ORTEP diagram not shown).[15] This and other results obtained for the reaction shown in Scheme 5, along with similar products obtained from other alcohols, are collected in Table 1.

The first two entries are as described above, the products of which have been subjected to X-ray analysis. Other aryl-substituted alkyne derivatives were obtained in slightly lower yields (entries 3–5), most likely due, in the latter two cases, to the additional polarity induced by the pyridine and pyrimidine groups, which rendered chromatographic separation more difficult.

Replacing the *N*-Boc group with *N*-acetyl (entries 6 and 7) had little effect, and only slightly lower yields were obtained under the same, non-optimised alkylation conditions. Again, we felt it worthwhile to check that this, albeit small, structural alteration had not affected the regiochemical outcome of the alkylation which, once again, appeared to give a single compound. The crystalline product from Table 1, entry 6 gave crystals amenable to X-ray analysis and the refined ORTEP diagram is shown in Figure 2,[16] which confirms that there was indeed no alteration in regiochemistry.

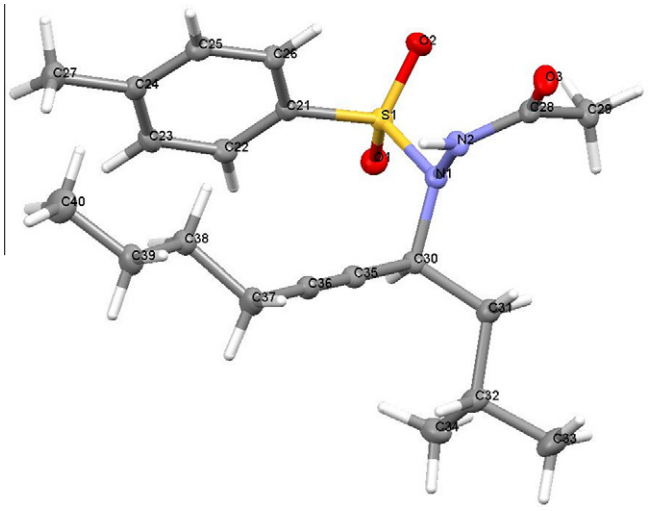


Figure 2. ORTEP diagram of the Mitsunobu adduct in Table 1, entry 6. CCDC 783434.

The presence of an alkyne function was not essential for successful alkylations, as expected. Thus, cinnamyl alcohol, prenyl alcohol and geraniol all underwent smooth alkylation of the unsymmetrical hydrazine TsNHNHCO$_2$Me (entries 8–10), as did a purely saturated alcohol (entry 11).

We have therefore shown that the original Ragnarsson conclusion, based entirely on considerations of pK_a values and two examples, was indeed correct despite an absence of a rigorous spectroscopic and analytical proof of structure. This should therefore encourage greater use of this efficient methodology for the synthesis of differentially substituted and differentially protected hydrazines, in this controlled, general and predictable manner.

Acknowledgments

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13. A typical procedure is as follows: *N-t-Butyloxycarbonyl-N′-(2-methyldec-5-yn-4-yl)-N′-p-toluenesulfonylhydrazine [17*; R^1 = ^{i}Bu, R^2 = Bu, R^3 = ^{t}OBu, Ar = *p*-MeC_6H_4] (Table 1, entry 1)—PPh_3 (11.71 g, 44.64 mmol) was added to stirred, anhydrous THF (450 ml) maintained under nitrogen and cooled in an ice-water bath. Once the solid had dissolved, diisopropyl azodicarboxylate (8.8 ml, 44.6 mmol) was added dropwise and the resulting solution stirred with continued cooling for 0.25 h. A white precipitate formed. 2-Methyldec-5-yn-4-ol [**16**; R^1 = ^{i}Bu, R^2 = Bu] (5.00 g, 29.8 mmol) was then added followed, after an additional 0.25 h, by *N*-Boc-*N′*-tosylhydrazine **13** (11.52 g, 44.64 mmol) resulting in formation of a clear orange solution. This was stirred overnight without the addition of further coolant and then the THF was evaporated. The residue was partitioned between EtOAc and H_2O. The separated aqueous layer was extracted with EtOAc (2 x) and the combined organic solutions were dried (Na_2SO_4), filtered and evaporated. The product was separated using silica gel column chromatography (10% EtOAc-hexanes) to give the *alkylated hydrazine* **17** [R^1 = ^{i}Bu, R^2 = Bu, R^3 = ^{t}OBu, Ar = *p*-MeC_6H_4] as a yellow solid (11.82 g, 91%), mp 59–60 °C (EtOAc-petrol), ν_{max}/cm^{-1} ($CHCl_3$) 3314, 2958, 2871, 1759, 1710, 1598, 1469, 1366, 1233, 1165, 1092; δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* = 8.0 Hz, 2 x ArH), 7.41 (2H, d, *J* = 8.0 Hz, 2 × ArH), 4.65 (1H, app. t, *J* = 7.4 Hz, 4-H), 2.42 (3H, s, Me), 2.05–1.97 (2H, m, 7-CH_2), 1.95–1.81 (1H, m, 2-H), 1.56 (2H, quin, *J* = 7.4 Hz, 8-CH_2), 1.49–1.28 (4H, m, 3- and 9-CH_2), 1.37 (9H, s, ^{t}Bu), 0.89 (3H, t, *J* = 7.1 Hz, 10-Me), 0.88 (6H, d, *J* = 7.0 Hz, 2 × Me); δ_C (100 MHz, $CDCl_3$) 144.3 (C), 129.5 (C), 129.2 (2 × ArCH), 128.5 (2 × ArCH), 89.1 (C), 81.3 (C), 50.4 (4-CH), 43.1 (CH_2), 30.4 (CH_2), 27.9 (3 × Me), 24.0 (2-CH), 21.9 (CH_2), 21.6 (CH_2), 21.4 (ArMe), 18.1 (Me), 13.5 (Me); *m*/*z* (ES) 454 (M + NH_4^+, 100%), 381 (25). Found: [M+NH_4^+] 454.2732. Calcd for $C_{23}H_{40}N_3O_4S$: *M*, 454.2740. Line broadening prevented definite observation of the C=O and quaternary ^{t}Bu carbon resonances.
14. The compound (Table 1, entry 1) crystallised in the triclinic space group P-1, with cell dimensions *a* = 8.58800(10) Å, *b* = 11.8690(2) Å and *c* = 13.1390(2) Å. The data were refined to an R value of 0.0467 and have been deposited in full at the Cambridge Crystallographic Data Centre, reference CCDC 783430, accessible at http://www.ccdc.cam.ac.uk.
15. The product **17b** (Table 1, entry 2) mp 134–135 °C, crystallised from ether–petrol in the monoclinic P21/a space group with cell dimensions of *a* = 8.9670(2) Å, *b* = 22.3460(6) Å and *c* = 12.9480(4) Å. The structure was refined to a final *R* value of 0.0537 and the full data set has been deposited at the Cambridge Crystallographic Data Centre, reference CCDC 783431.
16. The product from Table 1, entry 6, mp 62–63 °C, crystallised from EtOAc-petrol in the monoclinic P2/1n space group with cell dimensions of *a* = 15.7349(4) Å, *b* = 13.4711(2) Å and *c* = 20.1130(6) Å. The structure was refined to a final *R* value of 0.0586 and the full data set has been deposited at the Cambridge Crystallographic Data Centre, reference CCDC 783434.