MITSUNOBU TYPE C-N BOND FORMATION WITH 4,7-DIMETHYL-3,5,7-HEXAHYDRO-1,2,4,7-TETRAZOCIN-3,8-DIONE (DHTD), A NEW CYCLIC AZODICARBOXAMIDE

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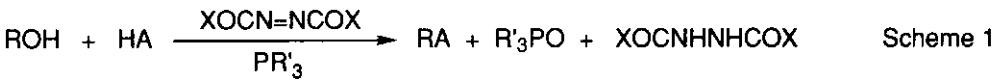
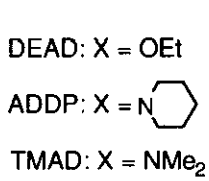
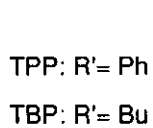
Abstract - The combination of 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) and tributylphosphine (TBP) was found to mediate successfully C-N bond formation between *N*-methyltosylamide, a typical *N*-nucleophile, and several alcohols of different structural types. The unique feature of this combination is that it activates the reaction of *sec*-alcohols at room temperature.

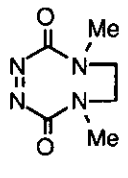
Recently we have developed several new azodicarboxamides to replace diethyl azodicarboxylate (DEAD) in the Mitsunobu reaction (Scheme 1) in order to improve the versatility of the original combination of DEAD and triphenylphosphine (TPP).[1] The azodicarboxamides introduced are 1,1'-(azodicarbonyl)dipiperidine (ADDP),[2] *N,N,N',N'*-tetramethylazodicarboxamide (TMAD)[3] and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD)[4] to be used with tributylphosphine (TBP). While



Scheme 1







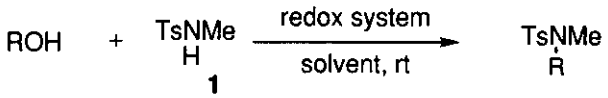
DHTD

Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

all of them are more versatile than DEAD, the cyclic DHTD was unique in mediating satisfactorily the formation of the C-C bond with *sec*. alcohols at room temperature.[4,5] Therefore, we investigated C-N bond formation using *N*-methyltosylamide (**1**, pK_a = 11.7[6]) as a nucleophile (HA).[7]

The reaction was carried out as described in the previous papers.[4] The results are shown in the Table below along with the acyclic counterparts.

Table 1. C-N bond formation (alkylation of **1**).

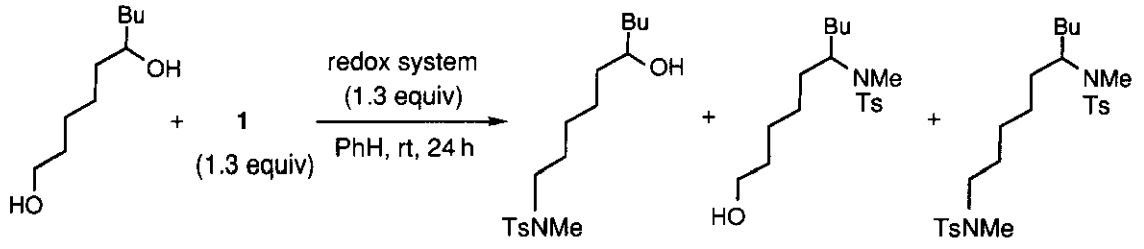


redox system	R				
	Bu-	$MeCH{=}CHCH_2$-	$PhCH_2$-	PhC_2H_4-	$C_6H_{13}CMeH$-
DEAD-TPP (THF)	65[a]	51[a]	66[a]	59	53[a]
TMAD-TBP (PhH)	100[a]	96[a]	99[a]	85	40[a]
DHTD-TBP (PhH)	100	97	97	94	85

a: Reported values (ref. 3)

The Table clearly demonstrates that 1) the combination of DHTD-TBP is as good as TMAD-TBP and both are better than DEAD-TPP for the reaction of *primary* alcohols, and 2) DHTD-TBP is far better than the other two for the reaction of 2-octanol, affording 2-octylamide in quite a satisfactory yield.[8] The reaction was shown using optically active 2-octanol to proceed with complete Walden inversion.

The difference in the reactivity of *primary* and *secondary* hydroxyl groups was demonstrated by the regioselective amidation of 1,6-decanediol. Thus, the alcohol and an excess of **1** react in the presence of a redox system (1.3 equivalent). The yields of the mono- and diamides are shown in Scheme 2.



DEAD-TPP	43%	6%	8%
TMAD-TBP	86%	<1%	3%
DHTD-TBP	91%	<1%	9%

Scheme 2

Thus, the DHTD-TBP reagent was shown to provide a new versatile methodology for the synthesis of secondary amines in general, when coupled with the known desulfurization reactions.[9]

REFERENCES AND NOTES

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2. T. Tsunoda, Y. Yamamiya, and S. Itô, *Tetrahedron Lett.*, 1993, **34**, 1639.
3. T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Itô, *Chem. Lett.*, 1994, 539.
4. T. Tsunoda, M. Nagaku, C. Nagino, Y. Kawamura, F. Ozaki, H. Hioki, and S. Itô, *Tetrahedron Lett.*, 1995, **36**, 2531. T. Tsunoda, C. Nagino, M. Oguri, and S. Itô, *Tetrahedron Lett.*, 1996, **37**, 2459.
5. DHTD was designed to prevent a serious side reaction (cyclization to an oxadiazole)[3] which occurred in this reaction when using acyclic azodicarboxamides.[4] The DHTD-TBP reagent was found to be a versatile Mitsunobu reagent system applicable to nucleophiles of pK_a up to ~13.5.[4]
6. G. Dauphin and A. Kergomard, *Bull. Soc. Chim. Fr.*, 1961, 486.
7. 4-Methyl-1,2,4-triazoline-3,5-dione (MTAD), another cyclic azodicarboxamide, has been applied to the Mitsunobu halogenation (T. Oshikawa and M. Yamashita, *Bull. Chem. Soc. Jan.*, 1984, **57**, 2675). In our hands, the 4-phenyl derivative (PTAD) (R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 1962, 615 and references cited therein) was found to be inactive in the present reactions. In this case, a small amount of 1-benzyl-4-phenyl-1,2,4-triazolidine-3,5-dione, an alkylation product of dihydro-PTAD, was obtained as a by-product in the reaction of benzyl alcohol.
8. Cyanomethylenetributylphosphorane which we have developed is also quite satisfactory in the same alkylation (T. Tsunoda, F. Ozaki, and S. Itô, *Tetrahedron Lett.*, 1994, **35**, 5081). However, it has a definite disadvantage; the reaction proceeds satisfactorily only when it is carried out at higher temperatures.
9. S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson, and P. Wriede, *J. Am. Chem. Soc.*, 1967, **89**, 5311. J. Kovacs, and U. R. Ghatak, *J. Org. Chem.*, 1966, **31**, 119.

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