Pergamon

Tetrahedron Letters 43 (2002) 5953–5956

TETRAHEDRON LETTERS

Regioselective and diastereoselective phosphine-catalysed [3+2] cycloadditions to 5-methylenehydantoins: reversal of regioselectivity using chiral *N*-2-butynoyl-(4*S*)-benzyloxazolidinone

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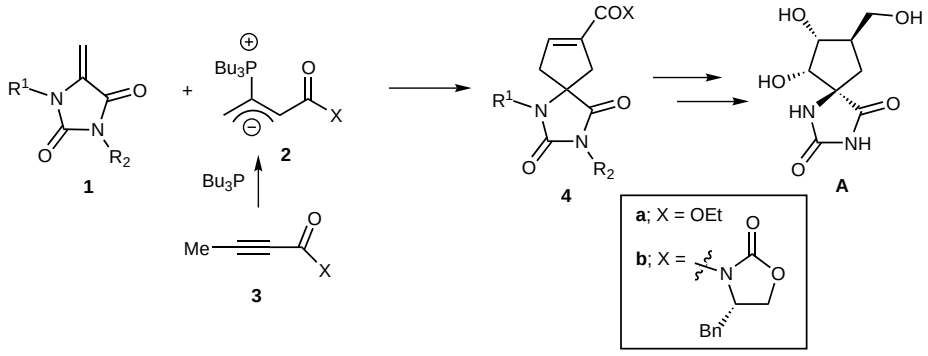
Received 6 June 2002; revised 24 June 2002; accepted 27 June 2002

Abstract—The phosphine-catalysed [3+2] cycloaddition of 5-methylenehydantoins **1** with the ylides **2a** and **2b** gives spirocyclic products with reverse regioselectivities; the latter ylide gives optically active products.

The phosphine-catalysed cycloaddition of ethyl buta-2,3-dienoate or ethyl butynoate with an electron-deficient alkene has been established as a useful method for preparing substituted ethyl 1-cyclopentenecarboxylates.[1–8] Optically active versions of these products can be obtained using either a chiral electron-deficient alkene,[5,8] giving spiro-heterocyclic derivatives, or a chiral phosphine catalyst.[6] As part of a project aimed at preparing carbocyclic analogues (**A**) of the potent herbicide, hydantocidin[9] we have examined the phosphine-catalysed [3+2] cycloaddition of 5-methylenehydantoins **1** with the ylides **2a** and **2b**, that were generated in situ from the reaction of ethyl butynoate **3a** and *N*-(2-butynoyl)-(4*S*)-benzyloxazolidinone **3b**, respectively, with tributylphosphine (TBP). Compounds **1** and **3b** have not been previously investigated as components for these types of cycloaddition reactions. Interestingly we have found that the ylide **2b** that was generated from **3b** gives optically active products with the reverse regioselectivity to that of the traditionally used ethyl butynoate **3a** (Scheme 1).

5-Methylenehydantoin **1** ($R^1=R^2=Bn$) and its *p*-methoxybenzyl (PMB) analogue **1** ($R^1=R^2=PMB$) were prepared using literature procedures.[10] The other 5-methylenehydantoins were prepared from 5-hydroxymethylhydantoin by selective *N*-benzylation (KOBu^t, BnCl, DMSO, rt, 1 h),[11] followed by treatment with Boc_2O (2.1 equiv.)/DMAP (0.2 equiv.)/MeCN, at rt for 18 h or Ac_2O (4 equiv.)/Et_3N (2 equiv.) at rt for 8 h.



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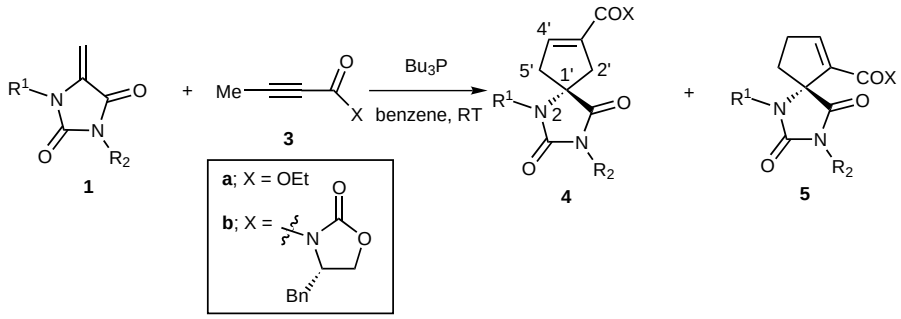


Scheme 1.

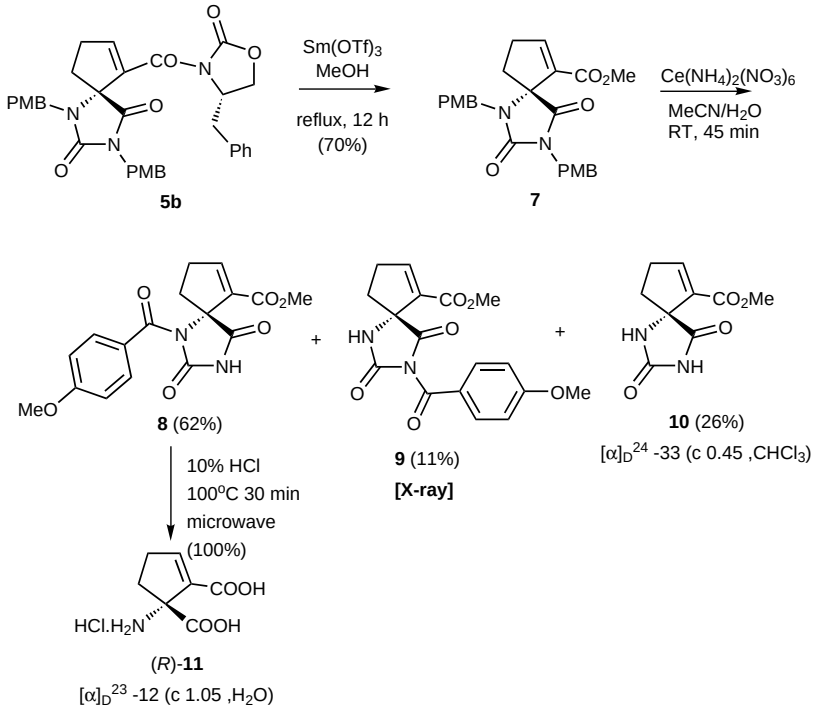
The ylide **2a** was generated in situ from the reaction of ethyl butynoate (2 equiv.) and TBP (0.1 equiv.) in the presence of **1** ($R^1=R^2=Bn$) in benzene solution at rt for 15 h. This reaction gave essentially a single regioisomer (**4a**) from ^1H NMR analysis of the crude reaction mixture. Column chromatography gave pure racemic **4a** in 81% yield based on the moles of **1** (Table 1, entry 1). The related triphenylphosphonium ylide was generated in situ from ethyl buta-2,3-dienoate[12a,b] (2 equiv.) and triphenylphosphine (0.1 equiv.) and reacted with **1** ($R^1=R^2=Bn$) to give an 80:20 mixture of the two regioisomers **4a** and **5a** that were readily separated by column chromatography (Table 1, entry 2). Pure **4a** and **5a** (both racemic) were obtained in yields of 65% and 17%, respectively. In general, regioisomers **4a**,**b** showed olefinic resonances upfield (δ 6.40–6.69) of the corresponding resonances for **5a**,**b** (δ 7.02–7.20).[13] The structures of **4a** and **5a** were determined by extensive 2D NMR studies. In particular, NOESY experiments on **4a** ($R^1=R^2=Bn$) showed cross peaks between the *N*-2 benzyl methylenes and H2′α and H5′α. While HMBC experiments revealed three bond-coupling between H2′β and H5′β, consistent with the small dihedral angle between these protons and C1.[14] The related PMB analogue **1** ($R^1=R^2=PMB$) gave a mixture of regioisomers in favour of the regioisomer **4a** ($R^1=R^2=PMB$). The major regioisomer could be isolated pure in 68% yield (Table 1, entry 3). The 1-Boc and 1-acetyl-3-benzyl-5-methylenehydantoins **1** ($R^1=Boc$ $R^2=Bn$) and **1** ($R^1=Ac$ $R^2=Bn$), respectively, also reacted with the ylide **2a** to give **4a** ($R^1=Boc$, $R^2=Bn$) and **4a** ($R^1=Ac$, $R^2=Bn$) as the major regioisomers, respectively (Table 1, entries 4 and 5).

In contrast, the 5-methylenehydantoin **1** ($R^1=R^2=Bn$) reacted with the ylide **2b**, that was generated in situ from the reaction of optically active (>98% ee) **3b**[15] (2 equiv.) and TBP (0.1 equiv.), in benzene solution at rt for 15 h to give a 11:89 mixture of **4b** and **5b** ($R^1=R^2=Bn$) (Table 1, entry 6). Diastereomerically pure **5b** ($R^1=R^2=Bn$) was isolated in 54% yield while **4b** ($R^1=R^2=Bn$) was obtained as a 1:1 mixture of diastereomers. The 5-methylenehydantoins **1** ($R^1=R^2=PMB$) and **1** ($R^1=$ Boc, $R^2=Bn$) also reacted with the ylide **2b** to give mixtures that favoured regioisomer **5b** over **4b** (Table 1, entries 7 and 8). The major regioisomers **5b** ($R^1=R^2=$ PMB) and **5b** ($R^1=$ Boc, $R^2=Bn$) were obtained as single diastereomers while the minor regioisomers **4b** ($R^1=R^2=PMB$) and **4b** ($R^1=$ Boc, $R^2=Bn$) were obtained as 1:1 mixtures of diastereomers.

Table 1. TBP-catalysed cycloaddition reactions between 5-methylene hydantoins **1** and alkynes **3a** and **3b** in benzene solution at rt

Entry	Hydantoin **1**		Alkyne **3**	Products	
	R^1	R^2		Yield (%)[b]	Ratio **4**:**5**[h] (de)[i]
1	Bn	Bn	**3a**	81	>98:<2
2	Bn	Bn	Allene[a]	82[c]	80:20
3	PMB	PMB	**3a**	86[d]	83:17
4	Boc	Bn	**3a**	57[e]	78:22
5	Ac	Bn	**3a**	43[e]	80:20
6	Bn	Bn	**3b**	61[f]	11 (0%):89 (>98%)
7	PMB	PMB	**3b**	39[g]	18 (0%):82 (>98%)
8	Boc	Bn	**3b**	43[e]	5 (0%):95 (>98%)

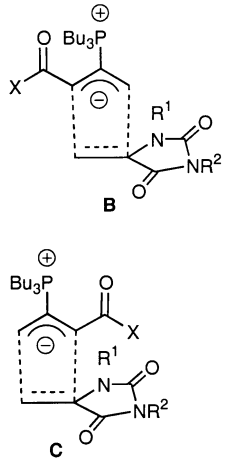
[a] Ethyl 2,3-butadienoate (2 equiv.) used with triphenylphosphine (0.1 equiv.).
[b] Combined yield of **4** and **5** after purification by column chromatography. Compounds **4a** and **5a** are racemic.
[c] Yield of **4** was 65%, yield of **5** was 17%.
[d] Yield of **4** was 68%, yield of **5** was 18%.
[e] Compounds **4** and **5** could not be separated.
[f] Yield of **4** was 7%, yield of **5** was 54%.
[g] Yield of **4** was 7%, yield of **5** was 32%.
[h] Determined by integration of the alkene resonances for **4** and **5**.
[i] Determined by ^1H NMR.



Scheme 2.

To determine the absolute stereochemistry of **5b** ($R^1 = R^2 = PMB$) the chiral auxiliary was removed by treatment with samarium(III) triflate in methanol[16] to give the methyl ester **7** in 70% yield (Scheme 2). Treatment of **7** with ceric ammonium nitrate in acetonitrile/water gave the desired *N*,*N*-dideprotected derivative **10** [($[\alpha]_D^{24}$ −33 (*c* 0.45, $CHCl_3$)] in 26% yield plus the mono-deprotected/benzylic oxidation products, the amides **8** (62%) and **9** (11%). Compound **9** formed single crystals from which its relative structure could be unequivocally determined by X-ray crystallographical structural analysis,[17] confirming our earlier regiochemical assignments of our cycloaddition products **5**. Microwave assisted acid hydrolysis of **8** using 1N HCl at 100°C for 30 min gave the known amino diacid **11**.[8] Its optical rotation ($[\alpha]_D^{23}$ −12 (*c* 1.05, H_2O) matched closely in magnitude that of the (*S*)-enantiomer (ee 88%) of this compound ($[\alpha]_D^{23}$ +11 (*c* 0.4, H_2O)[8] and the sign of the rotation indicated **11** had the (*R*) stereochemistry.

The difference in regiochemical outcomes between **2a** and **2b** with **1** suggests that electronic effects are responsible for the reversal of regiochemistry rather than steric effects. Based on steric considerations only, transition state **B** would be expected to be less sterically crowded and favoured over transition state **C** for both **2a** and **2b** (Scheme 3). Preliminary semiempirical calculations (AM1, PC Spartan Pro) on **2a** and **2b** suggest that the magnitude of the FMO coefficient of the HOMO of **2b** is significantly larger at the γ-position than that in **2a**, consistent with a reversing of the observed regiochemical outcomes.



Scheme 3.

Acknowledgements

We thank the University of Wollongong for a Ph.D. scholarship to T.Q.P.

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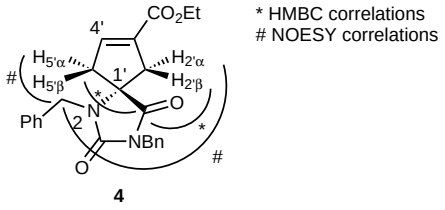
13. We believe the regioisomeric cycloaddition products are formed under kinetically controlled conditions since the diastereomeric product ratios were the same when the reactions were terminated before complete consumption of the starting hydantoin **1**.
14. 

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17. To be published in the full paper.