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Synthesis of an α-(Aminooxy)arylacetic Ester by the Reaction of an α-Diazo Ester with N-Hydroxyphthalimide.

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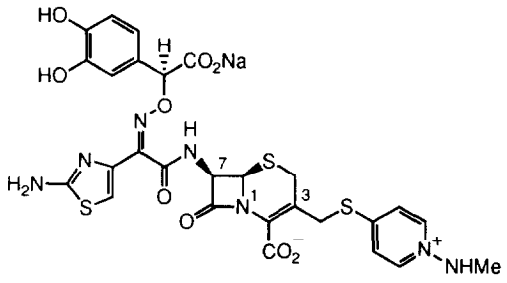
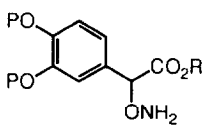
Abstract: The α-diazo esters (**6**) and (**7**) react, in the absence of any catalyst, with a variety of $HONR_2$ and $HON{=}CR_2$ compounds to give the *O*-alkylated adducts (**8**) to (**16**). In particular, reaction of (**7**) with N-hydroxyphthalimide in refluxing benzene followed by deprotection gives the title compound (**1**).

Recently, as part of a program of work looking at synthetic routes to the cephalosporin antibiotic **BRL 57342A**,[1] we were interested in the synthesis of the α-(aminooxy)ester (**1**) which is a key intermediate in the synthesis of the C-7 side chain of this and other cephalosporins.[2] Previous syntheses of targets of type (**1**) have evolved around either a Mitsunobu displacement on the corresponding α-hydroxy ester[3] or displacement of an α-halo ester or acid[4] with N-hydroxyphthalimide. We envisaged a new approach to the formation of the C-O(N) bond in (**1**) namely by reaction of the α-diazo ester (**2**) with a hydroxylamine or suitable synthetic equivalent. α-Diazo carbonyl compounds[5] are versatile intermediates and undergo rhodium-carbenoid mediated O-H insertion reactions with alcohols.[6,7] We considered whether such a reaction would also occur with N,N-disubstituted hydroxylamines.[8]

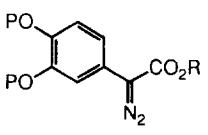


BRL 57342A

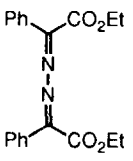


(**1**)

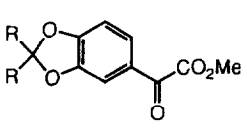
P = protecting group



(**2**)



(**3**)

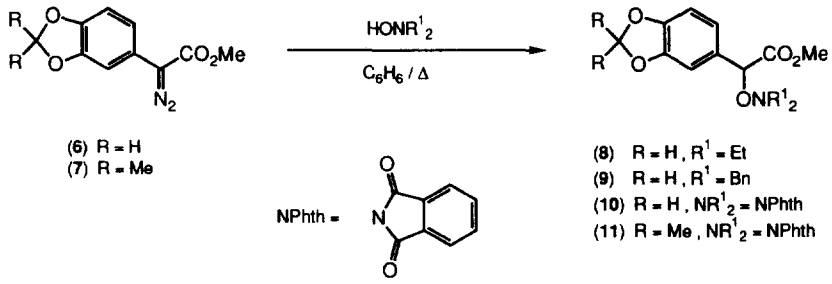


(**4**) R=H

(**5**) R=Me

As a starting point, and as a simple model, α-diazophenylacetic acid methyl ester was prepared.[9] When a solution of this diazo compound in dichloromethane was treated with a catalytic amount of rhodium(II) acetate (1 mol%) in the presence of N-hydroxyphthalimide only the dimeric product (**3**) was formed in 73% isolated yield. The α-diazo esters (**6**) and (**7**) were then synthesised from the α-keto esters[10] (**4**) and (**5**) by Bamford-Stevens base catalysed (Et_3N) decomposition of their corresponding tosyl hydrazones[5] in 87% and 69% yields respectively. Disappointingly when the α-diazo ester (**6**) was reacted with N-hydroxyphthalimide in benzene in the presence of a catalytic amount of rhodium(II) acetate a complex mixture resulted from which none of the desired adduct (**10**) could be detected. However, in the absence of any catalyst the α-diazo ester (**6**) reacted cleanly in refluxing benzene with N-hydroxyphthalimide, N,N-dibenzylhydroxylamine and N,N-diethylhydroxylamine to give the adducts (**8**) to (**10**) (see table). In the case of N,N-diethylhydroxylamine a small amount of the ketone (**4**) was also isolated. When the acetonide protected derivative (**7**) was reacted with N-hydroxyphthalimide a quantitative isolated yield of the adduct (**11**) was obtained.[11] Removal of the phthalimido protecting group with hydrazine gave the target compound (**1**) (P= acetonide protection, R= Me) in good yield.

Table : Reaction of the α-diazo esters (**6**) and (**7**) with $HONR^1{}_2$.[a)]



(**6**) R = H
(**7**) R = Me

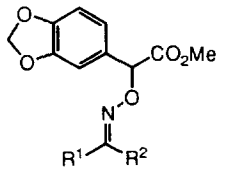
(**8**) R = H, R^1 = Et
(**9**) R = H, R^1 = Bn
(**10**) R = H, $NR^1{}_2$ = NPhth
(**11**) R = Me, $NR^1{}_2$ = NPhth

DIAZO COMPOUND	$HONR^1{}_2$ (mole equivalents)	PRODUCT (isolated yield)
(**6**)	$HONEt_2$ (3.0 eq.)	(**8**) (49%) (**4**) (19%)
(**6**)	$HONBn_2$ (3.0 eq.)	(**9**) (61%)
(**6**)	HONPhth (3.0 eq.)	(**10**) (57%)
(**6**)	HONPhth (1.0 eq.)	(**10**) (57%)
(**7**)	HONPhth (1.0 eq.)	(**11**) (100%)

a) *Typical procedure* : A mixture of the α-diazo compound (**6**) or (**7**) and $HONR^1{}_2$ in dry benzene is refluxed with stirring under a nitrogen atmosphere until the reaction is judged complete by tlc (silica gel, hexane-ethyl acetate, 3:1). The reaction mixture is evaporated to dryness and the product isolated by silica gel column chromatography.

In the light of these results the reaction of the α-diazophenylacetic acid methyl ester with N-hydroxyphthalimide was repeated in the absence of any rhodium catalyst. However, even after prolonged refluxing in benzene, no reaction was observed. This suggests that the oxygen atoms at positions 3 and/or 4 in the aryl rings of (**6**) and (**7**) are dictating the reactivity, and in the case of the 4 substituent the participation of a quinonemethide intermediate could be envisaged.

As described above the phthalimido protecting group can be removed with hydrazine. In search of alternative protecting groups we considered whether the α-diazo ester (**6**) would react with oximes.[12] The resultant substituted oxime could then be hydrolysed under acidic conditions to give the free α-(aminooxy)-ester (**1**). Alternatively since the C-7 side chain of **BRL 57342A** contains the oxime functionality, reaction of (**6**) with an appropriate thiazole hydroxyoxime would give the C-7 side chain directly. Indeed, it was found that oximes react with (**6**), again in the absence of any catalyst, although the reactions were not as clean as with the hydroxylamines. Thus refluxing (**6**) in benzene with acetone oxime, benzophenone oxime and cyclohexanone oxime afforded the adducts (**12**), (**13**) and (**14**) respectively in 34-40% yields after chromatography. In the case of acetone oxime and cyclohexane oxime the products were contaminated with a small amount (10%) of the α-keto ester (**4**) which was difficult to remove by chromatography. When the α-diazo ester (**6**) was reacted with syn-benzaldehyde oxime a mixture of the syn and anti adducts (**15**) and (**16**) was formed. The isomers were separated by chromatography and isolated in 33% and 5% yields but their stereochemistry was not determined.[13] Since the yields upon reaction with oximes were low this approach was not investigated further.



(**12**) $R^1 = R^2 = Me$

(**13**) $R^1 = R^2 = Ph$

(**14**) $R^1, R^2 = -(CH_2)_5-$

(**15**) $R^1 = H, R^2 = Ph$

(**16**) $R^1 = Ph, R^2 = H$

In conclusion, it has been shown that the α-diazo esters (**6**) and (**7**) react readily with a variety of $HONR_2$ and $HON{=}CR_2$ compounds in refluxing benzene to give the adducts (**8**) to (**16**). These reactions occur in the absence of any rhodium acetate catalyst. It remains to be seen how general this reaction is in terms of alternative α-diazo esters, but clearly the oxygen substituents in (**6**) and (**7**) play a major role. Using this approach the α-diazo ester (**7**) was reacted with N-hydroxyphthalimide and the resultant adduct (**11**) deprotected to give the target molecule (**1**), a key intermediate in the synthesis of the cephalosporin antibiotic **BRL 57342A**.

References and Notes

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   (b) Adams, R.G.; Brain, E.G.; Branch, C.L.; Guest, A.W.; Harrington, F.P.; Mizen, L.; Neale, J.E.; Pearson, M.J.; Simpson, I.N.; Smulders, H.; Zomaya, I.I. *J. Antibiotics*, **1995**, *48*, 417-424.
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7. Cox, G.G.; Kulagowski, J.J.; Miller, D.J.; Moody, C.J.; Sie, E.H.B. *Tetrahedron*, **1994**, *50*, 3195-3212.
8. To our knowledge there has been no literature reports of the successful reaction of an α-diazo ester with N,N-disubstituted hydroxylamines. There is however, one report in which ethyl diazoacetate is reacted with an N-hydroxy-2-azetidinone in the presence of rhodium(II) acetate but this afforded a complex mixture. See: Miller, M.J.; Woulfe, S.R.*J. Med. Chem.*, **1985**, *28*, 1447-1453.
9. Koga, K.; Mizoguchi, T.; Takamura, N.; Yamada, S. *Tetrahedron*, **1975**, *31*, 227-230.
10. The α-keto esters (**4**) and (**5**) were prepared in an analogous fashion to that reported in reference 3 above for the preparation of ethyl 2-(3,4-isopropylidenedioxyphenyl)-2-oxoacetate.
11. All compounds were characterised by mass spectroscopy, ^{1}H n.m.r. and ^{13}C n.m.r.
12. To our knowledge there are no literature reports of oximes reacting with α-diazo esters. There is an isolated report of a substituted diazo compound (diphenyldiazomethane) reacting with an oxime to give the substituted oxime. See: Isobaev, M.D.; Kostyanovskij, R.G.; Markov, V.I.; Mishchenko, A.I.; Pleshkova, A.P.; Prosyanik, A.V. *Izv. A.N. SSSR, Ser. Khim.*, **1979**, *HO 1*, 131-139.
13. The stereochemistry of the individual adducts was not unambiguously assigned, but the major adduct is believed to be the anti isomer based upon chemical shifts in the proton n.m.r.

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