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SYNTHESIS OF AZA-β-LACTAMS BY RHODIUM CARBENOID MEDIATED CYCLISATION

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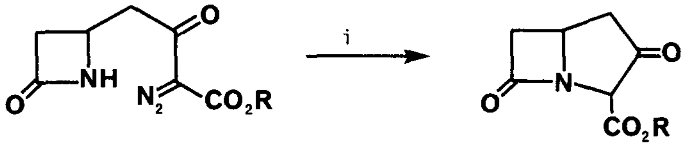
Summary: Treatment of the diazo-compounds (**3**), obtained in two steps from readily available hydrazine derivatives (**1**), with a catalytic amount of rhodium (II) acetate in benzene gives the aza-β-lactams (**4**) in high yield.

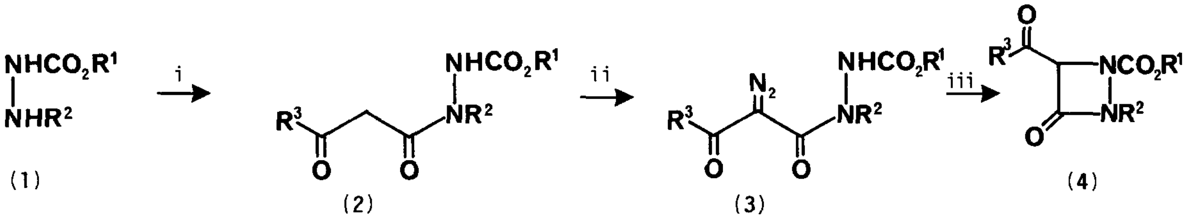
The decomposition of α-diazocarbonyl compounds has been widely studied under thermal, photochemical, and transition-metal catalysed conditions,[1] and the intramolecular cyclisation of the resulting carbenes or carbenoids can lead to synthetically useful reactions.[2] For example, intramolecular C-H insertion of α-diazoamides gives β-lactams by ring closure of the C3-C4 bond of the four-membered ring,[3] although probably the most significant intramolecular insertion reaction of recent years is the key step in the Merck synthesis of carbapenams (Scheme 1).[4]



Scheme 1. Reagents: i, $Rh_2(OAc)_4$, benzene, reflux.

Since rhodium (II) catalysed decomposition of diazo-compounds involves a rhodium carbenoid intermediate rather than a free carbene, the above type of ring closure is probably better regarded as nucleophilic attack by the lactam NH on the rhodium carbenoid, rather than an insertion into the N-H bond. We have exploited this principle of intramolecular nucleophilic attack on rhodium carbenoids in the synthesis of 1,2-diazetidinones, aza analogues of β-lactams,[5] and we report our results herein.

The starting materials are the readily available carbazates (**1**, R^1 = ^{t}Bu, R^2 = CH_2Ph)[6] and (**1**, R^1 = ^{t}Bu or CH_2Ph, R^2 = CH_2CO_2Et),[7] which are converted into aza-β-lactams (**4**) in three steps as shown in Scheme 2. Thus, acylation of the more basic nitrogen with ethyl malonyl chloride or with diketene gives the diacyl hydrazines (**2**) (68-100%), which, without purification, were subjected to the normal diazo-transfer conditions.[8] The diazo-compounds (**3**), isolated in variable yields (19-76%), were purified by chromatography, and cyclised in good yield (Table) to the aza-β-lactams (**4**) by treatment with a catalytic amount of rhodium (II) acetate in refluxing benzene.



Scheme 2. Reagents: i, EtO_2CCH_2COCl, Et_3N, benzene, or diketene, benzene; ii, TsN_3, Et_3N, CH_2Cl_2; iii, $Rh_2(OAc)_4$, benzene.

Table Aza-β-lactams (**4**) from Diazo-compounds (**3**)

Diazo-Compound	R^1	R^2	R^3	Aza-β-lactam	Yield(%)	$\upsilon_{max}(cm^{-1})$	δ H-4
(**3a**)	^tBu	CH_2Ph	OEt	(**4a**)	91	1805	5.23
(**3b**)	^tBu	CH_2Ph	Me	(**4b**)	100	1795	5.17
(**3c**)	^tBu	CH_2CO_2Et	OEt	(**4c**)	95	1820	5.40
(**3d**)	^tBu	CH_2CO_2Et	Me	(**4d**)	75	1820	5.32
(**3e**)	$PhCH_2$	CH_2CO_2Et	OEt	(**4e**)	93	1820	5.43
(**3f**)	$PhCH_2$	CH_2CO_2Et	Me	(**4f**)	82	1820	5.48

The aza-β-lactams (**4**) are colourless oils exhibiting their characteristic high frequency carbonyl stretch in the i.r. spectra, and low field singlet for H-4 in their ^1H n.m.r. spectra (Table).

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