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Synthesis of Pyrrolo[1,2-*a*]indoles by Intramolecular Heck Reaction of N-(2-Bromoaryl) Enaminones

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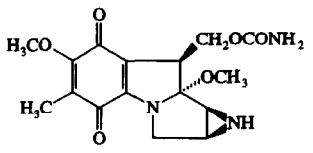
Abstract: Treatment of N-(2-bromoaryl) enaminones **4**, prepared by several different methods, with palladium(II) acetate, triarylphosphine and triethylamine in boiling acetonitrile gave pyrrolo[1,2-*a*]indoles **8** yields of 50% - 100%. The hydroxy-substituted product **8k** could be oxidised to the mitosene-like quinone **9** with Fremy's salt.

The mitomycins[1] (*e.g.* mitomycin A, **1**) constitute a small group of heterocyclic quinones having pronounced antibacterial and antitumour activity. Considerable effort has been devoted to the synthesis of these important *Streptomyces* metabolites, and to that of their biologically active degradation products, the mitosenes (*e.g.* **2**). Both classes of compound are characterised by the presence of a pyrrolo[1,2-*a*]indole nucleus, the construction of which has challenged organic chemists for nearly three decades[2,3]. We now report the synthesis of this tricyclic ring system by means of an intramolecular Heck reaction[4] on N-(2-bromoaryl) vinylogous urethanes **3** and related enaminones.



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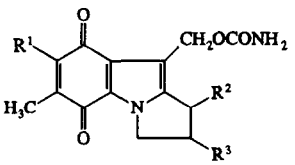

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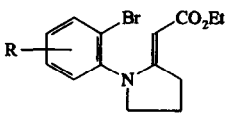
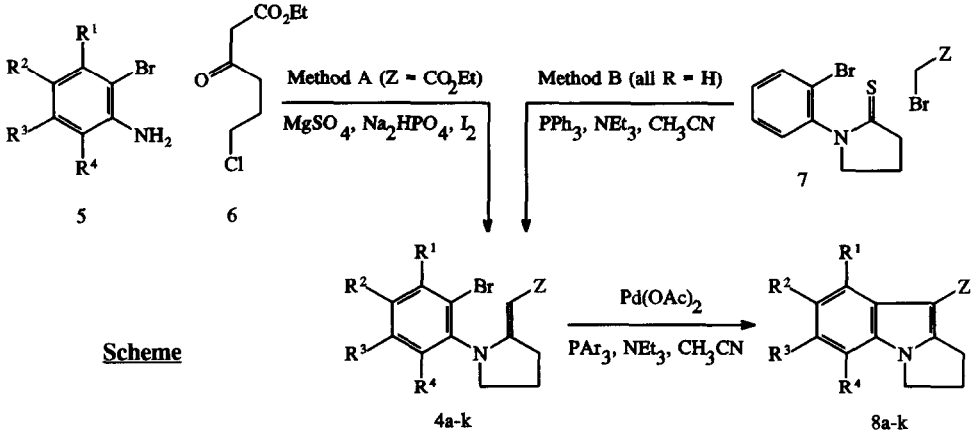


3

The strategy adopted exemplifies a new variant of our generalised approach to alkaloid synthesis *via* enaminone intermediates[5]. Whereas our past endeavours have exploited the nucleophilicity of N-alkylated enaminones related to **3** in cycloalkylation or cycloacylation processes, intramolecular attack on to an aromatic electrophile, as envisaged here, is a synthetically more demanding task. Fortunately, palladium-catalysed alkenylation of aryl halides by enamines and enaminones, while uncommon, is a known process; several indole syntheses[6-8] based on intramolecular Heck reaction of N-(2-haloaryl) enaminones serve as useful precedents for the desired ring closure depicted overleaf in the Scheme. A closer parallel is to be found in work by Luly and Rapoport[9], who applied the reaction to an N-(2-bromobenzoquinone) analogue of **3** in order to prepare the quinone version of the pyrrolo[1,2-*a*]indole system directly. These workers also observed the same kind of ring closure under photochemical conditions[10].

Two groups of substrates **4** were prepared for this study following methods we have previously reported[11] for making N-aryl vinylogous urethanes (Scheme, below). Substrates **4a-g** were chosen in order to examine the effect of varying the substituents on the aromatic ring while keeping the electron-withdrawing group Z constant as CO_2Et. A range of electron-donating substituents reminiscent of those present in the mitomycins and mitosenes was chosen for this study (R = H, CH_3, OCH_3). The compounds were formed by heating the appropriate *o*-bromoanilines **5**, made according to straightforward literature methods, with ethyl 6-chloro-3-oxohexanoate **6**[12] in the presence of magnesium sulphate, disodium hydrogen phosphate and a catalytic quantity of iodine (Scheme and Table, Method A). For compounds **4h-j**, in which the consequences of changing the group Z was to be explored, the aromatic ring was kept constant. In these cases, the Eschenmoser sulphide contraction procedure[13] with thiolactam **7** and appropriate α-halocarbonyl compounds (or bromoacetonitrile, for **4j**) offered more convenient access to the desired substrates (Method B). Compound **4k** was prepared by demethylating **4f** with boron tribromide (Method C).



Scheme

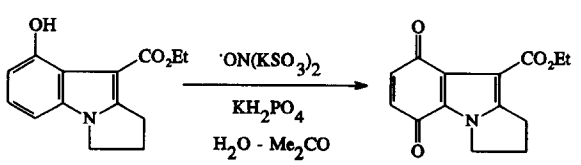
Standard Heck conditions (palladium(II) acetate, triarylphosphine, triethylamine, refluxing acetonitrile) were used to bring about the cyclisations reported in the Table. Two variables were found to have a significant influence on the outcome of the reaction: the nature of the phosphine, and the quantity of palladium acetate used. The effect was especially marked when the aromatic ring was loaded with electron-donating substituents, a feature known to retard Heck alkenylation of aromatic compounds[14]. Thus, for example, cyclisation to **8** could be extremely efficient when there were no additional substituents on the aryl ring (*e.g.* entry **a** in the Table). Yields decreased substantially as electron-donating groups were introduced, but could be boosted again if a stoichiometric, rather than catalytic, quantity of palladium(II) acetate was employed (*e.g.* entries **c**, **g**). There were significant improvements in yield when triphenylphosphine was replaced by the more hindered tri(*o*-tolyl)phosphine (*e.g.* entry **d**), a documented phenomenon ascribed to suppression of the competitive formation of tetraarylphosphonium salts[14]. Since optimum conditions for the formation of pyrrolo[1,2-*a*]indoles appeared to require both a stoichiometric quantity of the palladium salt and the use of the more hindered phosphine, most of the cyclisations were carried out in this way. It is to be noted that the reaction is successful even in the presence of a free phenolic substituent (entry **k**). Varying the nature of the electron-withdrawing group Z did not affect the course of the cyclisation, though some variability of yields was noted.

Table. Synthesis of N-aryl enaminones **4**, and cyclisation to pyrrolo[1,2-*a*]indoles **8**[15]

Entry	Synthesis of N-Aryl Enaminones **4a-k**			Heck reaction – pyrrolo[1,2-*a*]indoles **8**			
	Procedure,[a] yield (%)	R^1 - R^4	Z	$Pd(OAc)_2$ (eq)	PAr_3	Time (h)	Yield of **8** (%)
a	A, 41 (B, 66)	$R^1 = R^2 = R^3 = R^4 = H$	CO_2Et	0.2 1.0	PPh_3 PPh_3	25.5 25.5	98 100
b	A, 63	$R^1 = R^3 = R^4 = H$, $R^2 = Me$	CO_2Et	0.2	PPh_3	9	78
c	A, 40	$R^1 = R^4 = H$, $R^2 = R^3 = OMe$	CO_2Et	0.2 1.0	PPh_3 PPh_3	18 18	36 63
d	A, 51	$R^1 = Me$, $R^2 = R^3 = R^4 = H$	CO_2Et	0.2 0.2	PPh_3 $P(o\text{-Tol})_3$	24 19.5	0 81
e	A, 46	$R^1 = R^3 = H$, $R^2 = R^4 = Me$	CO_2Et	1.0	$P(o\text{-Tol})_3$	45	87
f	A, 38	$R^1 = OMe$, $R^2 = R^3 = R^4 = H$	CO_2Et	1.0	$P(o\text{-Tol})_3$	264	55
g	A, 31	$R^1 = R^3 = R^4 = H$, $R^2 = OMe$	CO_2Et	0.2 1.0	$P(o\text{-Tol})_3$ $P(o\text{-Tol})_3$	18 20	0 84
h	B, 88	$R^1 = R^2 = R^3 = R^4 = H$	$COCH_3$	1.0	$P(o\text{-Tol})_3$	96	66
i	B, 79	$R^1 = R^2 = R^3 = R^4 = H$	COPh	1.0	$P(o\text{-Tol})_3$	96	79
j	B, 94	$R^1 = R^2 = R^3 = R^4 = H$	CN	1.0	$P(o\text{-Tol})_3$	96	55
k	C, 51	$R^1 = OH$, $R^2 = R^3 = R^4 = H$	CO_2Et	1.0	$P(o\text{-Tol})_3$	120	50

[a]See text for methods A, B and C

In order to apply the methodology developed in this work to the synthesis of mitomycins and mitosenes, it must be possible to oxidise the aromatic ring of products **8**. The conversion of phenols into quinones upon treatment with Fremy's salt is a well-studied reaction[16], so tricyclic product **8k** was an obvious candidate for exploring quinone formation. When an acetone solution of **8k** was treated with the oxidant in water buffered with potassium dihydrogen phosphate, quinone **9** was indeed isolated as an unstable orange-coloured solid. However, the reaction could not be induced to go beyond 50% conversion. Even so, the isolated yield of **9** (48% based on recovered starting material) offers encouragement for future extension of these studies to the synthesis of mitosenes and aziridinomitosenes of greater biological interest.



8k **9**

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