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LETTERS

Metathesis of Aniline and 1,2-Dihydroquinoline Derivatives

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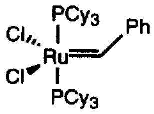
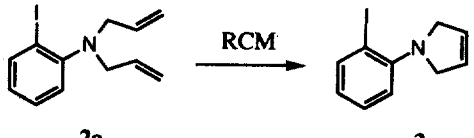
Abstract: Ring closing metathesis of *N,N*-diallylanilines and a related 1,2-dihydroquinoline, catalysed by Grubbs' catalyst, occurs in good yield at room temperature furnishing 3-pyrrolines and 3-piperidines. DCM and EtOAc are the solvents of choice and interesting substituent effects are identified and discussed. © 1999 Elsevier Science Ltd. All rights reserved.

The versatility of ring closing metathesis (RCM) for the construction of a wide variety of heterocycles has been amply demonstrated for small, medium and macrocyclic rings.[1] The most practical metathesis catalyst for general organic synthesis at present is Grubbs' catalyst **1**.[2] However, substrates possessing basic or nucleophilic nitrogen atoms suppress efficient catalysis[1,3] and such substrates must, as a rule,[4] be deactivated by conversion to amides / carbamates,[5,6b-c] sulfonamides[6] or by protonation.[7]



1



2a **3a**

It has been demonstrated that substituted *N*-heterocycles such as thiazole,[8] indole[9] and pyridine[6b] may be used in conjunction with **1**. Therefore, since anilines are, in general, only weakly basic with pK_a's < 5[10] this prompted a preliminary study of the RCM process **2a** → **3a** (Table 1).

Table 1. Solvent and Temperature Effects in RCM of 2a → 3a

Entry	$Cl_2(PCy)_2RuCHPh$ (**1**)	solvent	temp (°C)	time (h)	yield (%)[a] [**2a**:**3a**][b]
1	10 mol%	DCM	40	3	94[a]
2	2 mol%	DCM	40	12	93[a]
3	2 mol%	DCM	20	15	quant.[a]
4	2 mol%	THF	65	12	7:93[b,c]
5	2 mol%	THF	20	15	27:73[b]
6	2 mol%	PhMe	20	15	8:92[b]
7	2 mol%	MeCN	20	15	no reaction
8	2 mol%	DMF	25	15	87:13[b]
9	2 mol%	EtOAc	25	15	quant.[a]

[a]Isolated yields following column chromatography; [b]Ratio calculated from ^{1}H-NMR spectroscopy; [c]At elevated temperatures some pyrrole formation is observed.

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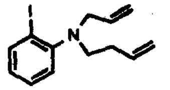
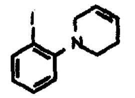
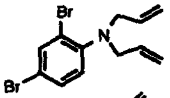
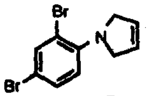
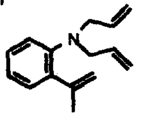
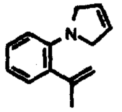
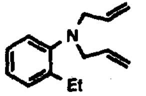
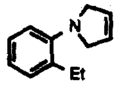
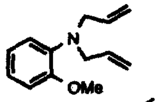
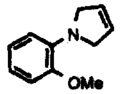
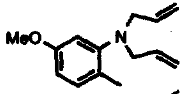
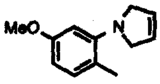
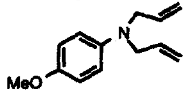
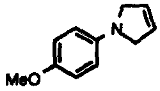
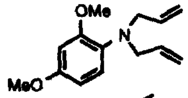
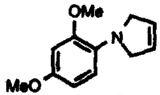
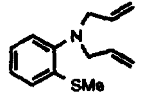
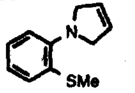
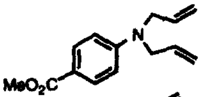
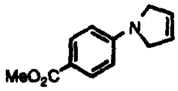
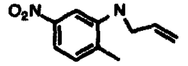
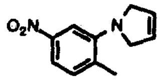
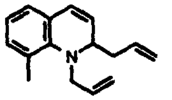
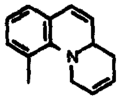
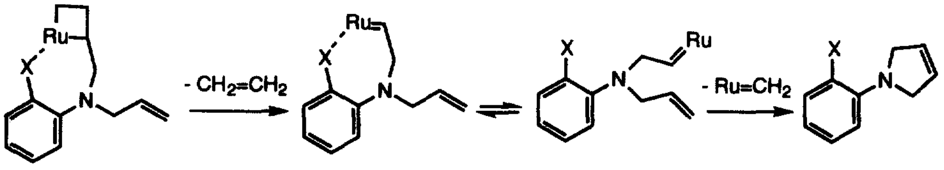
Table 2. Ring Closing Metathesis of 2b-2l and 4[a]

Entry	Substrate		Product		Yield (%)
1		2b		3b	83
2		2c		3c	98
3		2d		3d	80
4		2e		3e	44 (69)[b]
5		2f		3f	93
6		2g		3g	70
7		2h		3h	65
8		2i		3i	2i:3i; 71:29[c]
9		2j		3j	2j:3j; 90:10[c]
10		2k		3k	83
11		2l		3l	88
12		4		5	68 (95)[b]

[a] 2 mol% Grubbs 1, DCM (0.05 M), rt, 12 to 24 h; [b] yield based on recovered SM; [c] Ratio determined by ^{1}H-NMR spectroscopy; products not isolated due to low conversions under the standard optimum conditions.

It is clear from Table 1 that RCM of anilines is a viable process and that RCM of 2a occurs most efficiently at room temperature in DCM (Entry 3) or EtOAc (Entry 9). The latter observation will be of particular interest to process R and D chemists. The failure of the reaction in acetonitrile (Entry 7) indicates the incompatibility between this coordinating solvent and the catalyst 1. When the reaction was carried out in THF at 65°C (Entry 4) some dehydrogenation of 3a occurred, resulting in the formation of the corresponding pyrrole.

Following this initial success a variety of *N,N*-diallylanilines 2b-2l and the 1,2-dihydroquinoline 4 were investigated under the optimum DCM conditions.[11,12] The RCM process occurred in good to excellent yields in most cases (Table 2). The excellent yields in the case of the *ortho*-halo (Table 2, Entries 1 and 2) and *ortho*-vinyl (Table 2, Entry 3) anilines suggest these substituents promote the RCM by acting as "soft" donors to the ruthenium metal, see Scheme (where X = donor moiety).[13]



In contrast an *ortho*-ethyl group retards (steric effects dominant) the RCM process (Table 2, Entry 4). Table 2, provides evidence that a single methoxy-substituent (Entries 5, 6 and 7) does not impede the RCM process. In the cases of 2-methylthio (Entry 9) and 2,4-dimethoxyaniline (Entry 8) the RCM is strongly retarded. In the former case we presume the methylthio-substituent is sequestering the ruthenium species, thereby preventing catalyst recycling. The precise nature of the rate retardation in the case of the 2,4-dimethoxyaniline requires further study.

The location of electron withdrawing groups *meta* and *para* to the amino functionality (Table 2, Entries 10 and 11) allows the RCM to proceed to completion in excellent yield. Finally the RCM of the 1,2-dihydroquinoline 4 was carried out to assess the steric impact of the *peri*-methyl substituent (Table 2, Entry 12). The RCM was somewhat retarded but noticeably less so than the *ortho*-ethyl case (Table 2, Entry 4).

Future work on the processes described is in hand. We thank the EPSRC, Zeneca and Leeds University for support.

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11. Representative procedure: Solid Grubbs' catalyst **1** (18 mg, 0.022 mmol, 2 mol%) was added to the dialkenylaniline **2l** (254 mg, 1.1 mmol) dissolved in DCM (22 cm^3, 0.05 M) under argon at room temperature. Stirring was maintained for 15 h and the reaction was monitored by thin layer chromatography. The RCM 3-pyrroline **3l** (196 mg, 88%) product was obtained as an orange solid following flash column chromatography (petroleum ether-EtOAc; 9:1). m.p 68°C; δ_H ($CDCl_3$) 2.49 (3H, s, CH_3), 4.28 (4H, s, CH_2), 5.94 (2H, s, CH), 7.17 (1H, d, J 8.0 Hz, CH), 7.56-7.61 (2H, m, 2 x CH); δ_C ($CDCl_3$) 22.5 (CH_3), 57.8 (CH_2), 110.0, 114.1, 126.6, 133.1 (CH), 133.9, 147.7, 149.2 (C); Found C, 64.75; H, 6.10; N, 14.0%; $C_{11}H_{12}N_2O_2$ requires C, 64.7; H, 5.9; N, 13.7%; m/z (EI) 204 (M^+, 100%).

12. Synthesis of starting materials: RCM precursors **2a**, **2c** to **2l** were synthesised from commercially available anilines with allyl bromide. **2b** was prepared following initial treatment of 2-iodoaniline with 4-bromo-1-butene, then conversion of the initial monoalkylated aniline to **2b** with allyl bromide. **4** was prepared from 8-methyl quinoline by allyl Grignard addition and allyl bromide quench.

13. (a) Oxygen to ruthenium(IV) coordination: Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **1999**, *121*, 791; (b) bromine to tungsten(VI) coordination: Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.*, **1995**, *117*, 8992; (c) diethylether to tungsten(VI) coordination: Couturier, J. -L.; Tanaka, K.; Leconte, M.; Basset, J. -M.; Ollivier, J. *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 112.