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Copper(II)-Catalyzed [2,3]-Sigmatropic Rearrangement of *N*-Methyltetrahydropyridinium Ylids

Peter Heath,[†] Edward Roberts,[‡] Joseph B. Sweeney,*[,†] Hans Peter Wessel,[‡] and James A. Workman[†]

Department of Chemistry, University of Reading, Reading RG6 6AD, UK, and Hoffmann-La Roche Ltd., PRBC, Bldg. 92/8.92B, 4070 Basel, Switzerland

j.b.sweeney@reading.ac.uk

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Abstract: A ring-contractive and highly diastereoselective [2,3]-sigmatropic rearrangement occurs when *N*-methyl-1,2,3,6-tetrahydropyridine is treated with sub-stoichiometric amounts of copper or rhodium salts, in the presence of ethyl diazoacetate, giving ethyl *cis*-*N*-methyl-3-ethenyl proline (**4**).

Notwithstanding the initial observations by Stevenson et al. that the [2,3]-rearrangement reaction of carboxyl-stabilized ylids derived from *N*-methyltetrahydropyridine and bromoacetate are disfavored,[1] we recently reported the results of our reinvestigation of the base-induced [2,3]-sigmatropic rearrangements of ammonium ylids (**1**),[2] demonstrating that the reaction was subject to a pronounced solvent effect and that the rearrangement reaction *did* proceed, allowing the synthesis of a variety of *cis*-2-substituted-3-vinyl prolines (**2**, Scheme 1).[3]

This rearrangement process has great potential for the preparation of analogues of known neuroexcitators (such as kainoids, CPAA, and NMDA),[4,5] and we sought to investigate methods that would improve the efficiency of this reaction. Thus, in some cases, the product of elimination (**3**) was observed as a significant product in these reactions, whereas the intermediate ammonium salts that function as precursors to ylids (**1**) are, although simple to prepare, occasionally deliquescent materials, which complicates the experimental procedures involved. We also wished completely to suppress the side-reaction (viz., elimination); thus, we wished to investigate methods that would allow for a catalytic, metal-catalyzed method, believing that this type of reaction manifold would obviate these problems. We report here the details of the first phase of our investigations.

Doyle et al. had previously exploited rhodium catalysis in the nonasymmetric rearrangements of ammonium ylids derived from *acyclic* amines,[6] and we turned our attention to these data as the starting point in our quest. Thus, in mimicry of these prior observations, *N*-methyltetrahydropyridine was reacted with ethyl diazoacetate in refluxing dichloromethane, in the presence of rhodium acetate.[7]

To our surprise the reaction did not produce any of the expected product, under a range of conditions; indeed, other than the starting amine, no products could readily be identified from these reactions. When the process was carried out in benzene, again at reflux, a small yield of both rearranged product (**4**) and elimination product (**5**) was isolated from the reaction. When the addition of the diazo component of the reaction was accomplished via syringe pump (over a 33 h period), a 20% yield of **4** was isolated, accompanied by **5** (7% yield) (Scheme 2). The ^{1}H NMR spectra of the crude products of these reactions were complex, indicating (in addition to the desired product) the presence of a diverse mixture of species present in small amounts; the structures of these compounds have not yielded to further analytical investigations.

We next turned to the use of copper salts in this reaction, and we were gratified to observe a more efficient reaction when a solution of the same diazoester was added slowly (rate of addition 1.45 mL/h) to a suspension of amine and $Cu(acac)_2$ (20 mol %) in refluxing toluene: ethenyl proline (**4**) was isolated in 59% yield, as a single, *cis*-configured[8,9] diastereoisomer. We were also pleased to observe that no trace of the elimination product (**5**) was observed in the reaction.

We next set out to investigate the four key features of the reaction: the nature of the catalyst employed, the reaction temperature, the reaction solvent, and the rate of addition of the reagents. The data collected from these experiments are collated in Tables 1−3.

Our initial observations using a range of copper(II) salts indicated that $Cu(acac)_2$ was the most effective catalyst for the transformation (Table 1). Some of the data in Table 1 are worthy of further comment: first, the reaction does not proceed in the absence of catalyst (entries 1 and 2). In the latter reaction, a perusal of the ^{1}H NMR spectra of the crude reaction mixtures revealed a striking resemblance between this process and the first rhodium-catalyzed reaction described above.

Second, the yield of rearranged product decreased at the gain of the elimination product as the ligands become more electronegative through increasing fluorine substitution. This observation is in agreement with previous

[†] University of Reading.
[‡] Hoffmann-La Roche Ltd.

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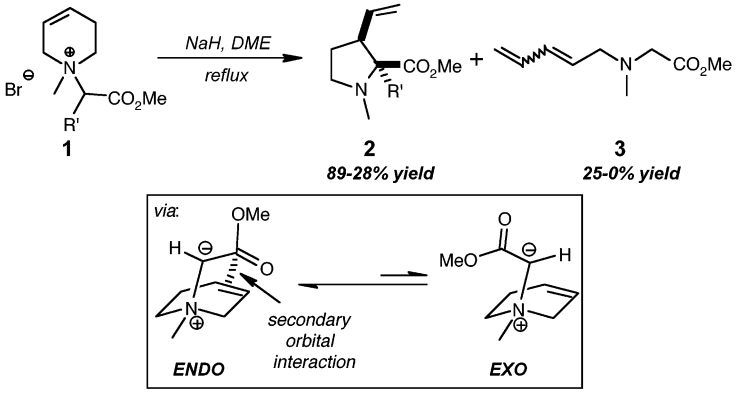
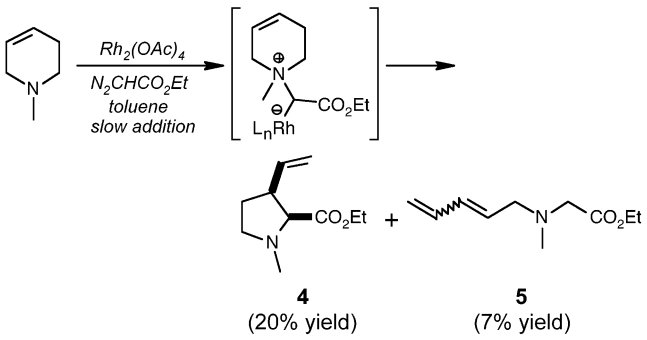
SCHEME 1. Base-Induced [2,3]-Sigmatropic Rearrangement of Tetrahydropyridinium Ylids

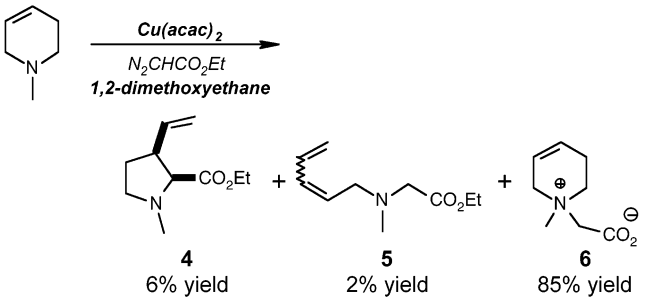


R'	Yield 2/%	Yield 3/%
H	59	5
Ph	71	3
1-Naphthyl	89	0
p-MeOC$_6$H$_4$	28	25
p-NO$_2$C$_6$H$_4$	48	0
p-ClC$_6$H$_4$	32	11
m-ClC$_6$H$_4$	43	9
m-FC$_6$H$_4$	36	0
p-FC$_6$H$_4$	58	0

SCHEME 2. Rhodium(I)-Catalyzed [2,3]-Rearrangement



SCHEME 3. Copper(II)-Catalyzed [2,3]-Rearrangement in 1,2-Dimethoxyethane



reports of the relative reactivity of fluorinated acetonylacetone catalysts, where increasing fluorination engendered increased reactivity at the expense of selectivity in metal-carbene processes.[10]

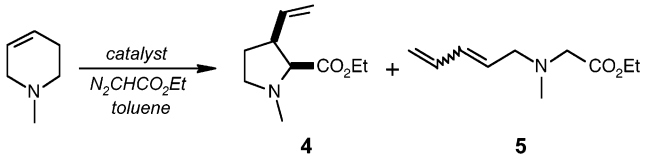
Having initially identified Cu(acac)$_2$ as the most effective catalyst, we next sought to investigate other factors affecting the reaction. Table 2 contains selected data concerning the effects of catalyst loading, solvent, and temperature upon the efficiency of the rearrangement process.

Again, two main conclusions can be made from analysis of these data: first, it seems that for efficient rearrangement a relatively high catalyst loading (≥10 mol %) must be employed. Second, there is a palpable solvent effect: the reaction generally proceeds in better yield when the reaction is carried out in non-oxygenated solvents. The effect is particularly noticeable when 1,2-dimethoxyethane was used as solvent, when rearrangement was not the major reaction pathway (entry 4 and Scheme 3). Instead the major product was 2-(*N*-methyl-1,2,3,6-tetrahydropyridinium)ethanoate (**6**), which was isolated in 85% yield. We are unable to devise a convincing explanation for the mechanistic origin of this compound at present.

The best yield of rearrangement was obtained when toluene was employed as solvent, conditions under which the yield of rearranged product was also maximized (Table 1, entry 7). The original, relatively high catalyst loading (20 mol %) proved most efficient in terms of rearrangement.

These observations are in accord with the observation that noncatalyzed tetrahydropyridinium salt rearrangements are significantly slower than the corresponding

TABLE 1. Effect of Catalyst Variation on [2,3]-Sigmatropic Rearrangement[a]



			yield (%)	
entry	catalyst (mol %)	solvent	**4**[b]	**5**
1	none[c]	benzene	0[d]	0[d]
2	none	toluene	0[d]	0[d]
3	Rh$_2$(OAc)$_4$[c] (5)	benzene	0[d]	0[d]
4	Rh$_2$(OAc)$_4$ (5)	benzene	20[e]	7[e]
5	Cu(acac)$_2$ (5)	toluene	46	0
6	Cu(acac)$_2$ (10)	toluene	50	0
7	Cu(acac)$_2$ (20)	toluene	59	0
8	Cu(tfacac)$_2$ (5)	toluene	41	tr[f]
9	Cu(tfacac)$_2$ (20)	toluene	39	tr[f]
10	Cu(hfacac)$_2$ (5)	toluene	44	19
11	Cu(hfacac)$_2$ (20)	toluene	16	14
12	Cu(OTf)$_2$ (5)	toluene	42	4
13	Cu powder (20)	toluene	*g*	0

[a] A toluene solution of ethyldiazoacetate was added via syringe pump at a rate of 1.45 mL/h to a solution of catalyst and amine in refluxing toluene (see Experimental Section). [b] Only *cis*-diastereomer was isolated, assigned on the basis of ^{1}H NMR (see refs 7 and 8). [c] Slow addition not used: components mixed and reaction heated to reflux. [d] Unidentifiable material isolated. [e] Reaction also yielded a complex mixture of unidentifiable products. [f] As judged from ^{1}H NMR. [g] Product present in trace amounts (as evinced by crude ^{1}H NMR), but inseparable from other, unidentifiable byproducts.

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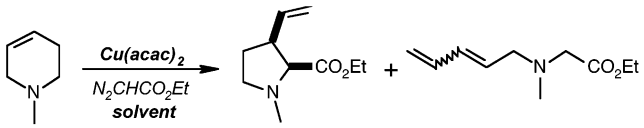
TABLE 2. Effect of Reaction Temperature, Catalyst Loading, and Solvent upon [2,3]-Rearrangement Catalyzed by Cu(acac)$_2$[a]

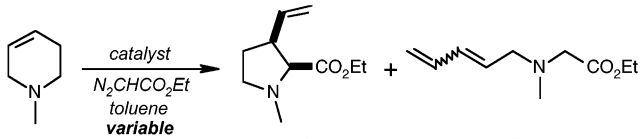


4 **5**

entry	Cu(acac)$_2$ (mol %)	solvent	temp (°C)	yield (%) **4**[b]	yield (%) **5**
1	5	CH_2Cl_2	40	0	0
2	5	Et_2O	35	0	0
3	5	THF	66	<3[c]	<5[c]
4	5	DME	85	6[d]	2
5	5	benzene	80	35	0
6	10	benzene	80	42	0
7	20	benzene	80	46	0
8	5	*p*-xylene	138	45	0
9	10	*p*-xylene	138	46	0
10	20	*p*-xylene	138	49	0

[a] A solution of ethyldiazoacetate was added via syringe pump at a rate of 1.45 mL/h to a solution of catalyst and amine in refluxing solvent (see Experimental Section). [b] Only *cis*-diastereomer was isolated, assigned on the basis of ^{1}H NMR. [c] Products not isolated; yields deduced from ^{1}H NMR spectra. [d] 2-(*N*-Methyl-1,2, 3,6-tetrahydropyridinium)acetic acid (**6**), isolated in 85% yield.

TABLE 3. Effect of Rate of Addition of Ethyldiazoacetate upon Yield of [2,3]-Rearrangement[a]



4 **5**

entry	catalyst (mol %)	addition rate (mL h^{-1})	yield (%) **4**[b]	yield (%) **5**	ratio (**4**/**5**)
1	Cu(acac)$_2$ (20)	2.89	42	0	
2	Cu(acac)$_2$ (20)	5.79	37	0	
3	Cu(tfacac)$_2$ (5)	2.89	55	11	5.0
4	Cu(tfacac)$_2$ (5)	5.79	46	10	4.6
5	Cu(hfacac)$_2$ (5)	2.89	43	25	1.72
6	Cu(hfacac)$_2$ (5)	5.79	35	17	2.1
7	Cu(OTf)$_2$ (5)	2.89	55	2	27.5
8	Cu(OTf)$_2$ (5)	5.79	36	<1	>36

[a] All reactions follow the general procedure with toluene used as solvent. [b] Only *cis*-diastereomer was isolated, assigned on the basis of ^{1}H NMR (see refs 7 and 8). [c] Assigned on the basis of ^{1}H NMR.

acyclic reactions;[9a] the reaction here is also further retarded by the increased ability of the tetrahydropyridine starting material to act as a Lewis base, inhibiting diazo decomposition through competitive association with the catalyst.

Given the relatively high catalyst loading required using Cu(acac)$_2$, we were motivated to reexamine the use of other (more active) catalysts in the process, specifically with a view to ascertaining the effect of alteration in the rate of addition of substrate upon the reaction. Table 3 summarizes the data accrued from these studies.

Two clear observations emerge from these data: first, in terms of conversion, it is clear that there is a different optimum addition rate for each type of copper(II) salt examined in the reaction, and second, the effect of the addition rate upon the yield of rearrangement depends intimately upon the ligand structure. Thus, increasing the rate of addition *diminishes* the efficiency of rearrangement using Cu(acac)$_2$ and Cu(hfacac)$_2$ but at first *enhances* rearrangement using Cu(tfacac)$_2$ and Cu(OTf)$_2$. In all cases using (more reactive and soluble) fluorinated ligands, lower catalyst loading is required.

We have demonstrated that the [2,3]-sigmatropic rearrangement of ammonium ylids derived from *N*-methyl tetrahydropyridine may be induced by a combination of ethyldiazoacetate and copper(II) catalysts. Using a range of reaction conditions, it was seen that the best yield of rearrangement was obtained using Cu(acac)$_2$ though the best results overall were obtained when Cu(II)(OTf)$_2$ was used as the catalyst, when the yield of rearrangement was similar but catalyst loading was much reduced (5 mol % rather than 20 mol %) compared to the Cu(acac)$_2$ reaction. The extrapolation of these data are currently the focus of the attention of our labs.

Experimental Section

General Procedure for Metal-Catalyzed Rearrangements. A solution of *N*-methyl-1,2,3,6-tetrahydropyridine hydrochloride (5.0 g, 37.4 mmol) in 2 M aqueous sodium hydroxide (56.1 mL, 112.2 mmol, 3 equiv) was extracted with pentane (4 × 25 mL). The combined organic extracts were dried ($MgSO_4$), and removal of solvent in vacuo gave *N*-methyl-1,2,3,6-tetrahydropyridine as a colorless liquid (2.98 g, 82%), which was used without further purification.

Catalyst (5−20 mol %) was added to a stirred solution of *N*-methyl-1,2,3,6-tetrahydropyridine in solvent (100 mL), under an atmosphere of argon. The reaction mixture was heated to reflux, and a solution of ethyldiazoacetate (total volume 50 mL) was added using a Razel syringe pump. When the additon of diazoester had been completed, the reaction mixture was cooled, diethyl ether (50 mL) was added, and the suspension was filtered. The solvent was then removed in vacuo, and the crude mixture was purified by column chromatography on silica gel, (eluting with diethyl ether/light petroleum [2:1]) to give varying amounts of *N*-methyl-2-ethoxycarbonyl-3-ethenylpyrrolidine (**4**) and ethyl-3-aza-3-methyl-octa-5,7-dienoate (**5**), both as oils.

***N*-Methyl-2-ethoxycarbonyl-3-ethenylpyrrolidine:** R_f 0.20; ν_{max} cm^{-1} ($CHCl_3$) 3080, 1641 (C=C), 1736 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (3H, t, *J* 7.1 Hz), 1.81 (1H, m), 2.04 (1H, m), 2.29 (1H, m), 2.30 (3H, s), 2.99 (1H, m), 3.06 (1H, d, *J* 8.3 Hz), 3.11 (1H, dt, *J* 1.9, 8.7 Hz), 4.11 (2H, dq, *J* 10.1, 7.2 Hz, OC**H**$_2$CH$_3$), 4.86 (1H, dd, *J* 1.5, 10.0 Hz), 4.96 (1H, dd, *J* 1.2, 17.1 Hz), 5.68 (1H, ddd, *J* 8.7, 10.0, 17.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.8, 31.0, 41.1, 46.6, 55.9, 60.8, 72.5, 116.2, 138.9, 171.9; *m*/*z* (CI) 184.1329 ([MH]$^+$, $C_{10}H_{18}NO_2$ requires 184.1337), 184 (100%), 110 (73%).

Ethyl-3-aza-3-methyl-octa-5,7-dienoate: R_f 0.30; ν_{max} cm^{-1} ($CHCl_3$) 3081, 1682, 1633 (C=C), 1736 (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* 7.1 Hz), 2.39 (3H, s), 3.25 (2H, s), 3.32 (2H, dd, *J* 1.4, 7.3 Hz), 4.19 (2H, q, *J* 7.1 Hz), 5.16 (1H, d, *J* 10.1 Hz), 5.25 (1H, dd, *J* 1.9, 16.8 Hz), 5.55 (1H, m), 6.18 (1H, m), 6.65 (1H, dddd, *J* 1.1, 10.1, 11.1, 16.8 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.7, 42.9, 54.0, 58.0, 61.0, 119.2 (**C**H$_2$=CHCH=CH), 128.4, 132.1, 133.0, 171.3; *m*/*z* (CI) 184.1343 ([MH]$^+$, $C_{10}H_{18}NO_2$ requires 184.1337, 184 (100%), 110 (48%), 67 (17%).

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Houllier, and J.A.W. wishes to dedicate his efforts to the memory of D. J. Workman, master craftsman.

Supporting Information Available: Detailed experimental procedures and ^{1}H NMR spectra for compounds **4**−**6** and representative experimental procedures for attempted asymmetric [2,3]-rearrangements. This material is available free of charge via the Internet at http://pubs.acs.org.

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