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Reaction of *N*-acetylimidazole with enamines

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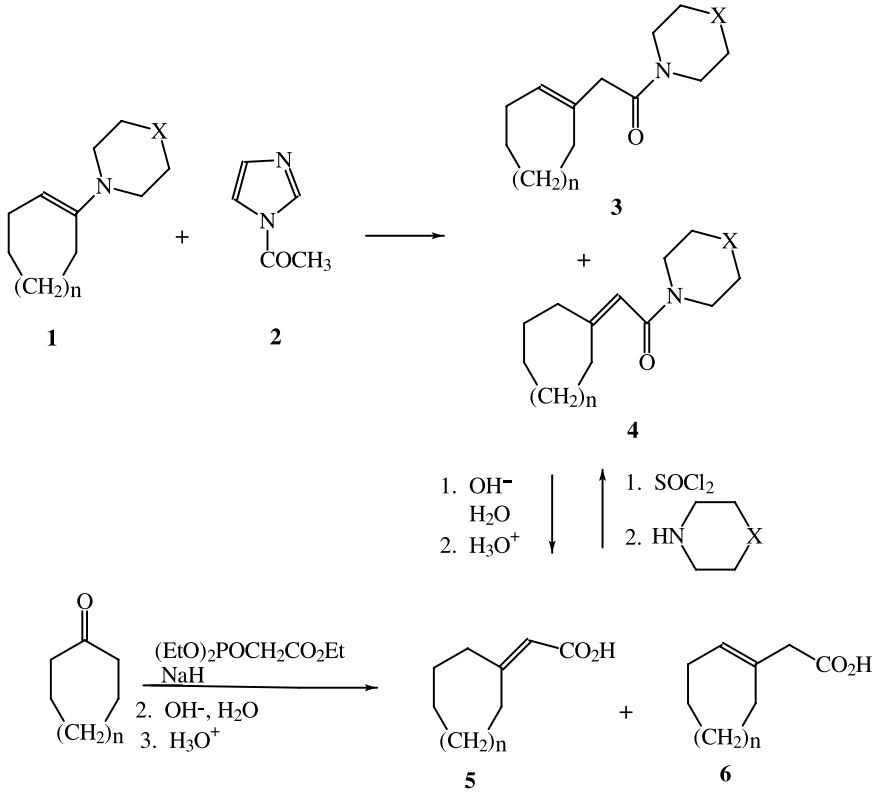
Abstract—*N*-Acetylimidazole is a commonly used acylating reagent. When it is allowed to react with several typical enamines, amides are produced rather than the expected acylated enamines.

Acylation of enamines using acid chlorides, acid anhydrides and ketenes has been well documented.[1,2] *N*-Acetylimidazole (**2**) is an azolide which has been used extensively for acylation of amines and alcohols.[3] However, there has not previously been a report of it being used to acylate enamines. We have found that *N*-acetylimidazole (**2**) does not simply acylate an enamine, but it undergoes a rearrangement to form an amide (Scheme 1). For example, when 1-(1-pyrrolidino)cyclohexene (**1b**) is allowed to react with *N*-



Scheme 1.

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Table 1. Reaction times, yields and physical properties of amides

Compound[a]	Ratio (*endo*(**3**):*exo*(**4**))	Yield (%)	bp °C (mm)	Time (min)
a	3:1	40	122–125 (0.3)	45
b	3:1	59	104–106 (0.6)	30
c	3:1	33	180 (3)	40
d	4:1	53	135–140 (0.45)	30
e	3:1	37	113–117 (0.3)	40
f	4:1	56	158 (0.3)	45

[a] **a** is X = bond, $n=0$; **b** is X = bond, $n=1$; **c** is X = CH_2, $n=0$; **d** is X = CH_2, $n=1$; **e** is X = O, $n=0$; **f** is X = O, $n=1$.

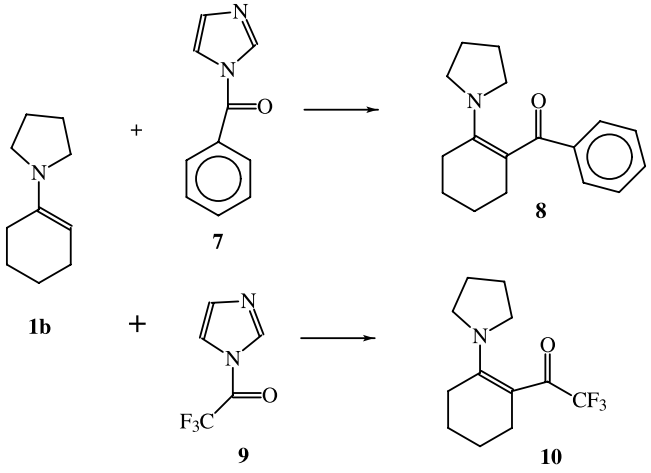
acetylimidazole at reflux temperatures, the only products isolated were 1-(1-cyclohexen-1-ylacetyl)pyrrolidine (**3b**) and 1-(2-cyclohexylidine-1-ylacetyl)pyrrolidine (**4b**)[4] in an overall yield of 59% and an isomer ratio of 3:1 of *endo* (**3b**) to *exo* (**4b**) (Table 1).

The structural identities of the amide products **3** and **4** were made as follows. One of the amide products, 4-(1-cyclohexen-1-ylacetyl)morpholine (**3f**), has previously been reported,[5] and the physical properties of **3f** correspond to those reported.[6] The amide products were hydrolyzed to produce the corresponding mixtures of previously reported acids, namely 1-cyclohexenylacetic acid[7] (**6**, $n=1$)/cyclohexylidene acetic acid[8] (**5**, $n=1$) and 1-cyclopentenylacetic acid[9] (**6**, $n=0$)/cyclopentylideneacetic acid[10] (**5**, $n=0$) (Scheme 1). These acids were synthesized by us using the known pathway of the Horner–Wadsworth–Emmons phosphonoacetate reagent[11] followed by hydrolysis of the ester. These independently synthesized unsaturated acids were then transformed into the desired amides using the standard technique of acyl halide production followed by treatment with a required secondary amine (Scheme 1). The products of these reactions had identical physical and spectroscopic properties as the products obtained from the reaction of *N*-acetylimidazole and the enamines.

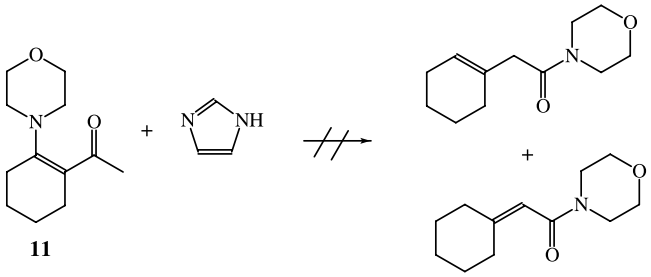
The use of *N*-acylimidazoles with no hydrogen on the α-carbon of the acyl group results in a normal acylation of the enamine. This is demonstrated by the treatment of 1-(1-pyrrolidino)cyclohexene (**1b**) with *N*-benzoylimidazole (**7**) to produce the simple acylated compound **8** in a 91% yield (Scheme 2). In a similar demonstration of this, the reaction of enamine **1b** with *N*-trifluoroacetylimidazole (**9**) produced addition compound **10** via an exothermic reaction at room temperature in a 47% yield. An acylation reaction of 1-(1-morpholine)cyclohexene with trifluoroacetic anhydride has been previously described.[12]

One possible pathway for this reaction to follow would be for the initial formation of acylated enamine **11**[13,14] followed by reaction with imidazole. However, allowing acylated enamine **11** to react with imidazole under identical reaction conditions *did not* produce the rearrangement products (Scheme 3).

Treatment of 4-methyl-1-pyrrolidinocyclohexene[15] (**12**) with *N*-acetylimidazole (**2**) produced amides (**13**) and



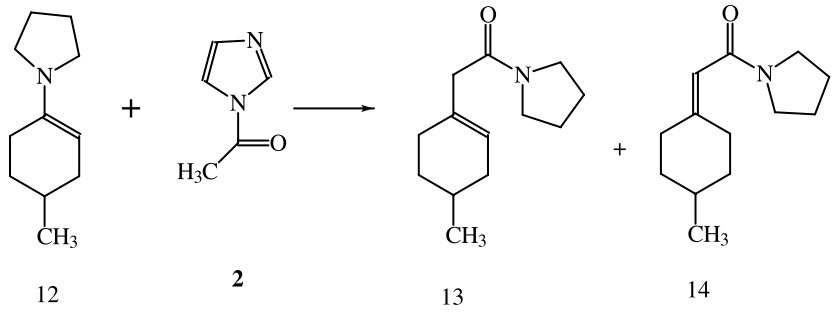
Scheme 2.



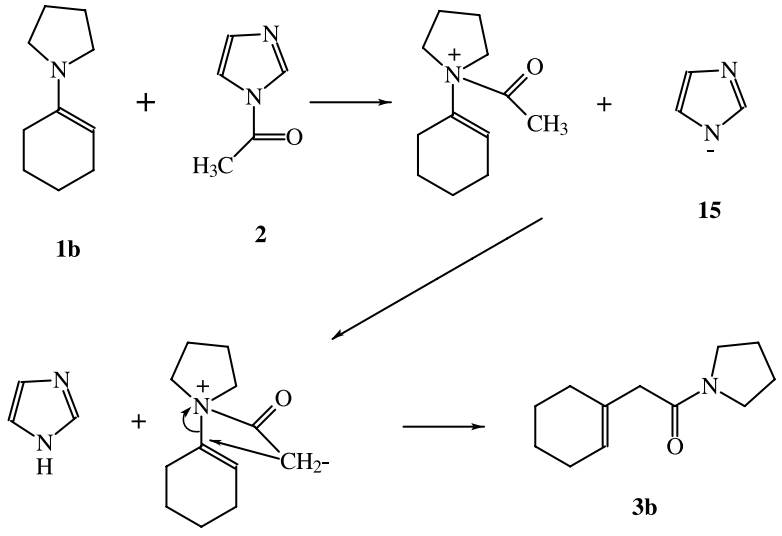
Scheme 3.

(**14**) in a 4:1 ratio (Scheme 4). The positioning of the amide group relative to the methyl group on the cyclohexane ring was shown by ^{13}C NMR.[16] This demonstrates that *ipso* substitution is taking place in this reaction.

A proposed mechanism for the formation of amide **3** is as shown in Scheme 5 using formation of **3b** as the example. There is a complete cleavage of the carbonyl–imidazole C–N bond in the first step of the mechanism producing imidazole anion **15** as a leaving group.[17] This anion is a strong enough base (pK_a 14.17)[18] to remove the α-proton from the acyl group attached to a positive nitrogen in the second step. This is followed by a rearrangement to give the final product amide **3b**.



Scheme 4.



Scheme 5.

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4. **3b**: IR spectrum (neat) ν_{max} 1626 cm^{-1}; ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) δ 1.40–1.60 (m, 4H), 1.95–1.79 (m, 8H), 2.90 (s, 2H), 3.35–3.44 (m, 4H), 5.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.18, 21.80, 23.43, 24.32, 25.24, 27.63, 43.51, 44.79, 45.87, 123.16, 130.74, 168.82; MS m/z (%) 193 (M^+, 25), 98 (M^+–95, 100), 55 (M^+–138), 53); **4b**: IR spectrum (neat) ν_{max} 1626 cm^{-1}, ^{1}H NMR spectrum ($CDCl_3$, 200 MHz) δ 1.40–1.60 (m, 4H), 1.95–1.80 (m, 10H), 3.35–3.44 (m, 4H), 5.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.99, 21.62, 23.0, 25.0, 26.62, 29.20, 36.37, 43.50, 45.90, 113.86, 154.85, 165.58; MS m/z (%) 193 (M^+, 75), 150 (M^+–43, 44) 123 (M^+–70, 100).
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16. **13**: ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.26, 23.95, 25.77, 27.66, 28.24, 30.57, 33.41, 43.82, 45.27, 46.36, 123.21, 130.85, 169.35.
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