Pergamon

Tetrahedron Letters 42 (2001) 7095–7098

TETRAHEDRON LETTERS

Highly selective synthesis of (*E*)-*N*-aryl-*N*-(1-propenyl) ethanamides via isomerization of *N*-allyl ethanamides catalyzed by ruthenium complexes

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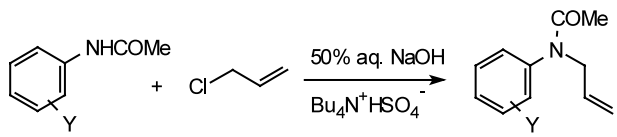
Received 6 June 2001; revised 2 August 2001; accepted 7 August 2001

Abstract—A convenient and highly selective method of synthesis of (*E*)-*N*-aryl-*N*-(1-propenyl)ethanamides via isomerization of respective *N*-allyl-*N*-arylethanamides catalyzed by [$RuClH(CO)(PPh_3)_3$] has been described. *N*-Allyl-*N*-arylethanamides have been obtained by allylation of respective *N*-arylethanamides under PTC conditions. It is proposed that the observed selectivity of the double bond migration to (*E*)-enamides is due to the interaction of the arene ring with the Ru atom in the transition state.

N-Propenyl amides (in general: *N*-vinyl amides) are interesting substrates mainly for synthesis of heterocyclic systems,[1–3] cycloaddition reactions,[4,5] reduction to enamines,[6] and are thoroughly investigated monomers and co-monomers.[7,8] Isomerization of *N*-allyl to *N*-propenyl amides is also a key step of protection and the following deprotection of amino groups.[9] The most convenient method for the synthesis of *N*-propenyl amides consists of isomerization of the appropriate *N*-allyl amides catalyzed by LDA[10,11] and, particularly, by transition metal complexes. Ruthenium,[12–15] iron,[12,15,16] cobalt[17] and rhodium[12,15,18] complexes have been used. Some enamides can also be synthesized via vinylation of amides by vinyl halides in the presence of nickel complexes[19] and by *N*-acylation of *N*-allyl imines.[6] *N*-Allyl amides (RCON(Ar)Allyl) were synthesized from amides (RCONHAr) by allyl bromide allylation under PTC conditions[20,21] in the presence of NaH[22] or NaOH in acetone.[23] *N*-Acylation of *N*-allylaniline[12,24] has also been used. In our earlier papers, we have described a series of examples of the synthesis of *O*-, *S*- and *N*-(1-propenyl) systems via isomerization of allylic compounds catalyzed by ruthenium and rhodium complexes.[25–31]

In the present work, we describe a convenient and very selective method of synthesis of various (*E*)-*N*-aryl-*N*-(1-propenyl) amides from the appropriate *N*-allyl amides via isomerization in the presence of [$RuClH(CO)(PPh_3)_3$] as the catalyst.

N-Allylamides were obtained by allylation of the respective amides by allyl chloride under PTC conditions.[32]



The following *N*-allyl-*N*-arylethanamides were obtained (isolated yield of $MeCON(Y\text{-}C_6H_4)Allyl$ in parentheses): Y = H (80%); *o*-Me (78%); *p*-Me (75%); *o*-MeO (81%); *m*-MeO (75%); *p*-MeO (81%); *o*-Cl (74%); *p*-Cl (76%); *o*-Br (80%); *p*-Br (82%). The purity of the synthesized *N*-allylamides (determined by ^1H NMR and GC–MS) was higher than 99.5%. This method of *N*-allylamide synthesis is simple and much more effective than those already known. It can also be applied to allylation of other N–H acids, such as carbazole and phthalimide. Pure (recrystalized) *N*-allylcarbazole and *N*-allylphthalimide have been prepared under the same conditions in yields of 85 and 80%, respectively. *N*-Allyl-*N*-(4-nitrophenyl)ethanamide was

Keywords: *N*-allylamides; selective isomerization; ruthenium complexes; (*E*)-enamides.

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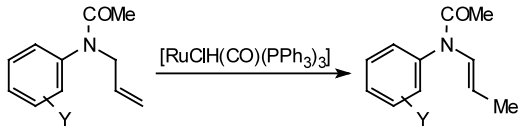
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01457-5

obtained by allylation of the corresponding amide by allyl bromide in the presence of KOH in acetone.[23] (*E*)-*N*-Aryl-*N*-(1-propenyl)ethanamides were obtained by isomerization of the respective *N*-aryl-*N*-allyl amides.[33]



The following pure (*E*)-*N*-aryl-*N*-(1-propenyl)-ethanamides were obtained (% isolated yield of MeCON(Y-C_6H_4)(1-propenyl) and % (*E*) selectivity in parentheses): Y = H (90, 99.0); Y = *o*-Me (95, 99.8); *p*-Me (93, 98.9); *o*-MeO (95, 99.3); *m*-MeO (92, 99.0); *p*-MeO (93, 98.9); *o*-Cl (95, 99.8); *p*-Cl (89, 98.9); *o*-Br (87, 99.5); *p*-Br (90, 98.8); *p*-O_2N (95, 99.3). The conversion of *N*-allyl amides to 1-propenyl derivatives was always quantitative (determined by ^{1}H NMR and GC–MS) and no by-products were observed. Therefore, the yields given are the yields of product separation. Moreover, in this reaction only (or almost only) (*E*)-enamides were formed. The configuration (*E*) of enamides synthesized was proven by X-ray crystallography,[34] e.g. the structure of (*E*)-*N*-(*p*-methylphenyl)-*N*-(1-propenyl)ethanamide (Fig. 1).

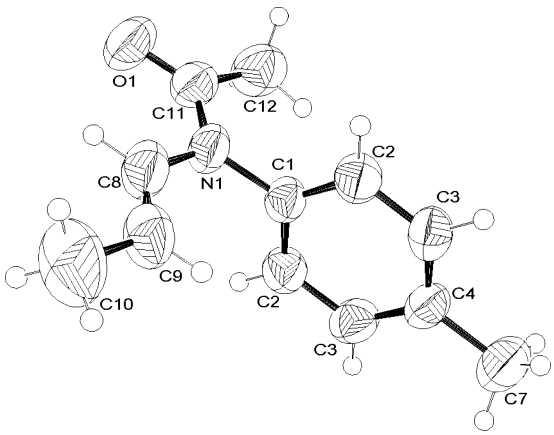


Figure 1. An ORTEP[38] view of the molecular structure of (*E*)-*N*-(*p*-methylphenyl)-*N*-(1-propenyl)ethanamide.[39]

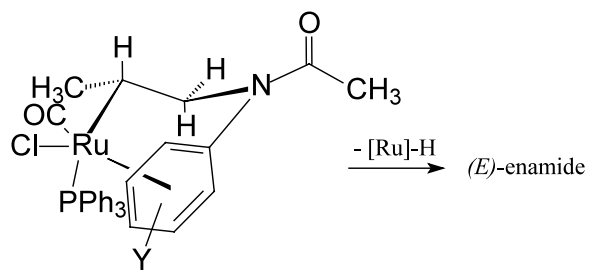


Figure 2. The formation of (*E*)-enamides as a result of coordination of the Ru atom by the aryl substituent (suggestion). We assume that the catalyst precursor loses two phosphine ligands. Other reaction steps are omitted.

We claim that the observed stereoselectivity cannot be explained by the higher thermodynamical stability of the *E*-isomer. Quantum calculations (AM1 method)[40] show that the *E*- and *Z*-isomers differ in their heat of formation by only 10.52 kJ/mol. An analysis of the shapes of the HOMO and LUMO of the (*E*)-*N*-phenyl-*N*-(1-propenyl)ethanamide (in the optimal conformation, determined by the AM1 method) proves the possibility of interaction between the Ru atom and the arene ring during the reaction. According to the calculations, the HOMO is essentially different from zero both in the aliphatic fragment and in the aromatic one, whereas the LUMO is different in the arene fragment only. It means that a back-bonding can form between the Ru atom and the arene ring in the course of the reaction (see Fig. 2), which leads to the formation of (*E*)-isomers. We have assumed that the double bond migration catalyzed by [$RuClH(CO)(PPh_3)_3$] occurs according to the hydride mechanism, as in the case of alkenes and allyl ethers.[25]

We have found that isomerization of Me-CONRAllyl (where R = H, allyl or cyclohexyl) catalyzed by [$RuClH(CO)(PPh_3)_3$] leads to the formation of a mixture of (*Z*)-, (*E*)-, or (*Z*,*Z*)-, (*E*,*E*)-, (*Z*,*E*)-enamides (isomerization conditions as before; quantitative conversion). The result of MeCONRAllyl isomerization is particularly important for R = cyclohexyl. Although the cyclohexyl substituent is very large (its steric effect is bigger than Ph) an (*E*)- and (*Z*)-enamides mixture is formed. This result indicates that the observed high selectivity of the Me-CONArAllyl isomerization steams from the coordination and not steric effects. Moreover, in the isomerization of RCONHAllyl of $RCONAllyl_2$ (R = Me or Me_3C) a mixture of isomers is also formed. This means that the increase in steric effect of the acyl group has no effect on the selectivity. It is clear now that the isomerization of $RCONR^1$ (allyl) is selective (i.e. (*E*)-enamides form) if and only if R^1 is an aryl.

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32. **Synthesis of *N*-allyl-*N*-arylethanamides (general method)**: The amide (0.2 mol), 50% aq NaOH (50 cm^3), $Bu_4N^+HSO_4^-$ (0.002 mol) and an excess of allyl chloride (50 cm^3) was intensively stirred and refluxed in a water bath for 4 h. After cooling, 100 cm^3 of water was added and an excess of allyl chloride was removed by distillation from the water bath. The residue was extracted twice with 100 cm^3 of hexane (or pentane). Then the extract was dried with anhydrous magnesium sulfate and decolorized by active coal. After distilling off all volatiles with a vacuum evaporator, the residue was distilled under reduced pressure (0.5–1 mmHg). *N*-Allyl-*N*-(*p*-methylphenyl)ethanamide, bp = 125–126°C/1 mmHg; ^{1}H NMR (C_6D_6): $\delta = 6.97$ (AA′XX′, 2H, -C_6H_4-), 6.86 (AA′XX′, 2H, -C_6H_4-), 5.89 (ddt, 1H, $J = 16.5$, 10.1, 6.3 Hz, -H_2C=C<u>H</u>-CH_2), 4.97 (dd, 1H, $J = 10.1$, 1.4 Hz, H_2C=CH-C<u>H_2</u>-*cis*), 4.96 (dd, 1H, $J = 16.5$, 1.4 Hz, -H_2C=CH-C<u>H_2</u>-*trans*), 4.31 (dd, 2H, $J = 6.1$, 1.2 Hz, -<u>H_2C</u>=CH-CH_2), 2.12 (s, 3H, *p*-C_6H_4-C<u>H_3</u>), 1.78 (s, 3H, NCOC<u>H_3</u>). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 169.7$ (-N<u>C</u>OCH_3), 140.5 ($C_{1\text{-arom}}$), 137.5 ($C_{4\text{-arom}}$), 133.4 (-H_2C-<u>C</u>H=CH_2), 130.1 ($C_{3\text{-arom}}$ and $C_{5\text{-arom}}$), 127.8 ($C_{2\text{-arom}}$ and $C_{6\text{-arom}}$), 117.5 (-H_2C-CH=<u>C</u>H_2), 51.9 (-H_2<u>C</u>-CH=CH_2), 22.5 (-NCO<u>C</u>H_3), 21.0 (Ar-CH_3). MS (EI, 70 eV) *m*/*z*: $M^+ = 189$ (62), 174 (9), 146 (100), 132 (52), 120 (90), 118 (41), 91 (92), 84 (35), 77 (55), 65 (62), 51 (18), 43 (83%).
33. **Synthesis of (*E*)-*N*-aryl-*N*-(1-propenyl)ethanamides (general routine)**. *N*-Aryl-*N*-allyl amide (0.1 mol) and [RuClH(CO)(PPh_3)$_3$] (0.5% mol) were heated at 120°C for 2 h (*o*-Cl and *o*-MeO 16 h) under an argon atmosphere. After cooling to room temperature, 300 cm^3 hexane (or benzene–hexane, 1:1) was added and the mixture was cooled to 0°C. The precipitated ruthenium compounds and PPh_3 were filtered off. The filtrate was chromatographed in a column containing 5 g of silica gel (200–400 mesh). Hexane was evaporated from the eluate in a vacuum evaporator. (*E*)-*N*-(*p*-Methylphenyl)-*N*-(1-propenyl)ethanamide: ^{1}H NMR ($CDCl_3$): $\delta = 7.46$ (d, 1H, $J = 14.1$ Hz, -<u>HC</u>=CH-CH3), 7.26 (AA′XX′, 2H, -C_6H_4-), 7.05 (AA′XX′, 2H, -C_6H_4-), 4.42 (dq, 1H, $J = 14.1$, 6.8 Hz, HC=C<u>H</u>-CH_3), 3.30 (s, 3H, p-C_6H_4-C<u>H_3</u>), 1.75 (s, 3H, -NCOC<u>H_3</u>), 1.43 (dd, 3H, $J = 6.8$ Hz, $J = 1.5$ Hz, -HC=CH-C<u>H_3</u>). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 168.3$ (-N<u>C</u>OCH_3), 138.4 ($C_{1\text{-arom}}$), 137.5 ($C_{4\text{-arom}}$), 130.5 ($C_{3\text{-arom}}$ and $C_{5\text{-arom}}$), 129.0 (-H<u>C</u>=CH-CH_3), 128.5 ($C_{2\text{-arom}}$ and $C_{6\text{-arom}}$), 108.9 (-HC=<u>C</u>H-CH_3), 23.1 (-NCO<u>C</u>H_3), 21.1 (Ar-CH_3), 15.0 (-HC=CH-<u>C</u>H_3). MS (EI, 70 eV) *m*/*z*: $M^+ = 189$ (35), 174 (9), 147 (80), 132 (68), 118 (21), 105 (13), 91 (35), 77 (12), 65 (37), 51 (15), 43 (100), 39 (48%).
34. Single-crystal X-ray diffraction analysis of (*E*)-*N*-(*p*-methylphenyl)-*N*-(1-propenyl)ethanamide. All measurements of diffraction intensities were performed on a KUMA KM4 four-circle diffractometer, Zr foil filtered Mo Kα radiation, $\omega/2\Theta$ scan mode.[35] The structures were solved by direct methods using the program SHELXS-97[36] and refined by full-matrix least-squares with the aid of the program SHELXL-97.[37] All non-hydrogen atoms were refined anisotropically. The hydrogen positions were calculated according to the standard geometry, and refined as a riding model with isotropic thermal parameters.[37] Crystal data for (*E*)-*N*-(*p*-methylphenyl)-*N*-(1-propenyl)ethanamide). The crystal chosen for X-ray analysis was a clear colorless plate with approximate dimensions 0.2×0.4×0.4 mm. $C_{12}H_{15}NO$ (189.25 g mol^{-1}) crystallizes in the monoclinic system, space group $P2_1/m$, with $a = 10.632(2)$, $b = 6.854(1)$, $c = 16.068(3)$ Å, $\beta = 106.35(3)°$, $V = 1123.6(3)$ Å^3, $Z = 4$, μ(Mo Kα) = 0.07 mm^{-1}, and $D_{calcd} = 1.119$ g cm^{-3}. The e.s.d. unit cell parameters were determined by least-squares refinement using 60 centered reflections within $2° < \Theta < 16°$. A total of 1695 reflections were collected to $2\Theta_{max} = 47.92°$ (*h*: 10→10, *k*: 0→7, *l*: 0→11), of which 1493 were unique. The intensity decay of the reference reflections was 34%. In refinements, weights were used according to the scheme $w = 1/[\sigma^2(F_o^2) + (0.0753P)^2 + 0.50P]$, where $P = (F_o^2 + 2F_c^2)/3$. The refinement of 158 parameters (data-to-parameter ratio being 9.45) has led to the final agreement factors $R = 0.0529$, $R_w = 0.1573$,

and $S=1.002$ for 897 observed reflections with $F>4\sigma(F_o)$. The electron density of the largest difference peak was found to be 0.24 e $Å^{-3}$, while that of the largest difference hole was 0.20 e $Å^{-3}$. Tables of bond distances and angles, atomic coordinates, and anisotropic thermal parameters of (*E*) - *N* - (*p* - methylphenyl) - *N* - (1 - propenyl)ethanamide (CCDC 162490) have been deposited with the Cambridge Crystallographic Data Centre.

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40. The calculation has been carried out with the AM1 method[41] of MOPAC 2000.[42] The stop criterion was to achieve a gradient less than 0.1 by the EF following vector optimisation method.[43]
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