Direct *N*-Allylation of Amides with 2-Allylisourea Catalyzed by Palladium(0)

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Synopsis. Direct *N*-allylation of amides catalyzed by palladium(0) complexes took place under neutral conditions by the use of 2-allylisourea as the allylating agent.

Direct alkylation of amides using reagents such as alkyl halides or sulfonates under neutral conditions generally leads to a mixture of *O*- and *N*-alkylated product. In order to obtain pure *N*-substituted amides, it is usually necessary to generate the amide anion by the use of strong base such as sodium amide or sodium hydride before treatment with alkylating agent.[1] Recently, it was informed that alumina coated with potassium fluoride was effective in promoting *N*-alkylation of amides.[2] The alkylation of amides with alcohols in the presence of ruthenium catalyst has also been reported.[3] Very lately, palladium-catalyzed reaction of allylic substrates with sodium *p*-toluenesulfonamide was shown to afford *N*-allylic derivatives.[4] In a previous paper,[5] we have reported the palladium-catalyzed direct α-allylation of ketones with 2-allyl-1,3-dicyclohexylisourea (**1**), obtained from the reaction of allyl alcohol with dicyclohexylcarbodiimide.[6] Herein we report a novel direct *N*-allylation of amide with **1** under neutral conditions.

The *N*-allylation of amides was performed generally as follows: A solution of **1** (1 eq.), an amide (1 eq.), [Pd(dba)$_2$](2 mol%)[dba=dibenzylideneacetone], and dppe (2 mol%)[dppe=$Ph_2PCH_2CH_2PPh_2$] in dry *N*,*N*-dimethylformamide (DMF) was stirred at 60—100 °C for 1—2 h under nitrogen atmosphere. Usually the progress of the reaction was conveniently monitored

$$CH_2{=}CHCH_2OH + CyN{=}C{=}NCy \longrightarrow CH_2{=}CHCH_2OC(NCy)(NHCy)$$

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$$RCNH_2 + \mathbf{1} \xrightarrow[-(NHCy)_2CO]{Pd(0)} RCNH(CH_2CH{=}CH_2) + RCN(CH_2CH{=}CH_2)_2$$

(cy = cyclohexyl)

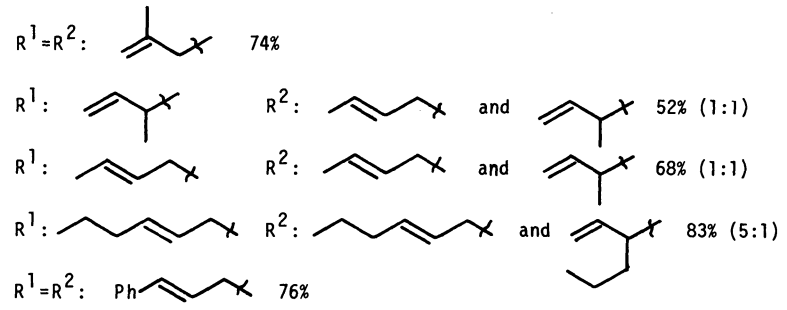
by the deposition of 1,3-dicyclohexylurea formed. The occurrence of *N*-allylation over *O*-allylation was confirmed spectroscopically by comparing with an authentic sample. Use of [Pd(PPh$_3$)$_3$] complex as the catalyst instead of [Pd(dba)$_2$]-dppe did not give rise to the product. Results are given in Table 1. Various amides were allylated in moderate to good yields. For primary amides, mono- and diallylation took place. The sulfur counterpart of acetanilide, *i.e.*, thioacetanilide, was selectively *S*-allylated. Toluenesulfonamide (*o*- and *p*-) could be readily *N*-allylated at 25 °C by this method. In this case, exclusive diallylation occurred.

$$CH_3CONHPh + R^1OC(NCy)(NHCy) \xrightarrow[100\,^\circ C,\ 1\ h,\ DMF]{[Pd(dba)_2]\text{-dppe}} CH_3CONR^2Ph$$

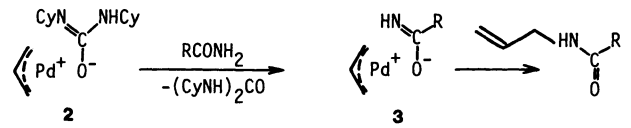
Table 1. Allylation of amide[a]

Amide	Reaction temp/°C	Reaction time/h	Product	Yield[b]/%
CH_3CONH_2	60	2	CH_3CONHR	45[c]
			CH_3CONR_2	37[c]
$PhCONH_2$	60	1	PhCONHR	27
			$PhCONR_2$	48
$CH_3CONHPh$	100	1	$CH_3CONRPh$	67
$CH_3CSNHPh$	25	0.25	$CH_3(RS)C{=}NPh$	60
$CH_2{=}C(CH_3)CONH_2$	60	2	$CH_2{=}C(CH_3)CONHR$	20
			$CH_2{=}C(CH_3)CONR_2$	40
2-Pyrrolidone	60	1	*N*-Allylpyrrolidone	86[c]
Caprolactam	60	1	*N*-Allylcaprolactam	87[c]
o-$CH_3C_6H_4SO_2NH_2$	25	1	*o*-$CH_3C_6H_4SO_2NR_2$	62
p-$CH_3C_6H_4SO_2NH_2$	25	1	*p*-$CH_3C_6H_4SO_2NR_2$	65

a) 2-Allylisourea (5 mmol), amide (5 mmol), [Pd(dba)$_2$] (2 mol%), dppe (2 mol%), DMF (10 cm^3); R = allyl.
b) Isolated yield, based on 2-allylisourea. c) GLC yield.



The reaction of several 2-allylic-substituted isoureas with acetanilide was also investigated. For the allylic system bearing a bulky substituent, the less substituted end tended to react preferentially. Unfortunately, a γ,γ-disubstituted allyl derivative, *i.e.*, 2-prenylisourea, did not undergo the reaction. 1-Methyl-2-propenyl- and 2-butenylisourea realized the same composition of the possible two products. This may indicate that both reactions proceed *via* a same intermediate.[7] Although the mechanism of the reaction is not so clear, we propose a tentative pathway *via* (π-allyl)palladium intermediate **2**, which is derived from oxidative addition of 2-allylisourea **1** to palladium(0). The isourea anion thus formed is supposed to be basic enough to abstract an amide proton to afford imidate intermediate **3**. Then reductive coupling gives the observed product.



2 3

Experimental

Preparation of 2-Allylic-substituted Isoureas. They were prepred from allylic alcohols and dicyclohexylcarbodiimide in the presence of a catalytic amount of cuprous chloride according to the published method.[6]

Allylation of Amides. An amide (5 mmol) was allowed to react with 2-allyl-1,3-dicyclohexylisourea (5 mmol) in dry DMF (10 cm^3) in the presence of [Pd(dba)$_2$](0.1 mmol) and dppe (0.1 mmol) under the conditions cited in Table 1. After the reaction was complete, water was added to the mixture. The product was extracted with ether and purified by column chromatography on silica gel. Certain samples for spectroscopic analyses were obtained by preparative GLC. They were denoted by asterisk(*) in the following.

Allyl N-Phenylthioacetimidate: An oil. IR (neat) 1628, 1127, 980, 910, 770, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.84 (s, 3H), 3.61 (d, 2H), 4.81—5.32 (m, 2H), 5.51—6.22 (m, 1H), and 6.25—7.28 (m, 5H); MS (70 eV) *m/z* 191 (M^+), 176, 118, 85, 83, and 77.

N-(2-Methyl-2-propenyl)acetanilide: An oil. IR (neat) 1660, 1380, 1275, 900, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.74 (s, 3H), 1.80 (s, 3H), 4.29 (s, 2H), 4.71 (s, 1H), 4.82 (s, 1H), and 7.06—7.65 (m, 5H); MS (70 eV) *m/z* 189 (M^+), 174, 147, 146, 132, and 106.

*N-(2-Butenyl)acetanilide**: An oil. IR (CCl_4) 1660, 1370, 970, and 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.60 and 1.71 (tentatively assigned to (*Z*)- and (*E*)-CH_3C=C, respectively, d, 3H (1:2)), 1.82 (s, 3H), 4.06—4.30 (m 2H), 5.28—5.58 (m, 2H), and 6.94—7.48 (m, 5H) MS (70 eV) *m/z* 189 (M^+) 146, 132, and 93.

*N-(1-Methyl-2-propenyl)acetanilide**: An oil. IR (neat) 1660, 1495, 1385, 1000, and 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.12 (d, 3H) 1.79 (s, 3H), 4.84—5.00 (m, 1H), 5.08—5.22 (m, 1H), 5.23—6.12 (m, 2H), and 6.86—7.50 (m, 5H); MS (70 eV) *m/z* 189 (M^+), 174, 146, 132, and 93.

N-(2-Hexenyl)acetanilide: An oil. IR (neat) 1660, 1387, 1265, 960, and 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.80 (t, 3H), 1.00—1.60 (m, 2H), 1.80 (s, 3H), 1.80—2.15 (m, 2H), 4.25 (d, 2H), 5.35—5.60 (m, 2H), and 7.13—7.55 (m, 5H); MS (70 eV) *m/z* 217 (M^+), 174, 146, 132, and 93.

*N-(1-Propyl-2-propenyl)acetanilide**: An oil. IR (CCl_4) 1660, 1495, 1380, 995, and 925 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (t, 3H), 1.16—1.58 (m, 4H), 1.74 (s, 3H), 4.84—5.92 (m, 4H), and 7.02—7.58 (m, 5H); MS (70 eV) *m/z* 217 (M^+), 174, 133, 132, and 93.

N-Cinnamylacetanilide: An oil. IR (neat) 1625, 1432, 1406, 1250, 962, and 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.76 (s, 3H), 4.35 (d, 2H), 6.13—6.37 (m, 2H), and 6.90—7.42 (m, 10H); MS (70 eV) *m/z* 251 (M^+), 208, 160, 117, and 115.

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7) In order to obtain stereochemical information on this reaction, we prepared an optically active 2-allylic-substituted isourea derived from *l-cis*-carveol,[8] and submitted to the reaction with acetanilide. However the only product isolated was a triene, 2-methyl-5-isopropenyl-1,3-cyclohexadiene. Exclusive 1,4-elmination took place.

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