A New Convenient Method for the Preparation of Enamides from *N*-Allylamides

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Abstract: Isomerization of various *N*-allylamides in the presence of $Fe(CO)_5$ smoothly afforded the corresponding enamides in yields up to 95%. The reported procedure is compatible with various functional groups including protected amino and hydroxy groups. The possible mechanism of transformation is discussed.

Key words: enamides, *N*-allylamides, double bond shift, iron pentacarbonyl

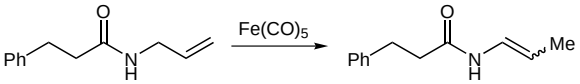
Enamides (*N*-alken-1-ylamides) are the interesting substrates for various transformations, including cyclopropanation,[1] Diels–Alder cycloaddition,[2] hydroformylation,[3] Paternò–Büchi photocycloaddition.[4] The first example of enamide-olefin ring-closing metathesis was recently published.[5] The simplest and most general method for the synthesis of *N*-substituted enamides is the acylation of aldo- or ketoimines with acyl halide or acid anhydride.[6–8] Secondary enamides are not so trivially available as their tertiary analogs. Several methods for their synthesis[9–13] were reported, but the yield of enamides is often modest. In addition, conditions used are in many cases quite harsh, making such procedures hardly suitable for the synthesis of the highly functionalized molecules.

Isomerization of *N*-allylamides to enamides is very attractive because *N*-allyl amides are readily available via standard synthetic methods.[14] Stille and Becker[15] reported isomerization of several simple *N*-allylamides to a mixture of (*Z*)- and (*E*)-enamides in moderate to high yield in the presence of hydridorhodium or -ruthenium complexes. However, a general catalyst could not be found, and it was necessary to match the reaction conditions with a particular substrate to reach an acceptable yield of enamide. In addition, catalysts used are not easily available and extremely air sensitive. In this paper we wish to report convenient and general procedure for the preparation of *N*-alken-1-ylamides from *N*-allylamides upon the action of commercially available, inexpensive, and stable $Fe(CO)_5$.[16]

Little was hitherto known about the isomerization of allylamides with this catalyst and the data are unpromising. Hubert et al.[17] reported the attempted photochemical isomerization of *N*-allylacetamide in the presence of $Fe(CO)_5$. Synthetic value of this method is limited, because it led to the equilibrium mixture of isomeric enamides with starting material, which was impossible to separate. Stille and Becker reported in the above mentioned publication,[15] that attempts to isomerize *N*-(3,3-dimethylallyl)-acetamide resulted in the decomposition of the starting material.

We have found, however, that the action of $Fe(CO)_5$ on *N*-(prop-2-enyl)-3-phenylpropanamide (**1a**) resulted in complete conversion of the starting material to the mixture of (*Z*)- and (*E*)-*N*-prop-1-enylamides **2a**, **2a′**. Reaction conditions were initially examined to optimize the yield of the enamides. We were pleased to find that at 100 °C the transformation of *N*-allylamide to *N*-prop-1-enylamide can be performed in almost quantitative yield (Table 1, entry 3). At lower temperatures complete conversion was not achieved in reasonable time (entries 1, 2), while at higher temperatures decomposition was essential and the yield was lower (entries 4, 5).

Table 1 Isomerization of *N*-(Prop-2-enyl)-3-phenylpropanamide (**1a**) in the Presence of $Fe(CO)_5$[a]



1a **2a** (*E*), **2a'** (*Z*)

Entry	Temp (°C)	Yield (%)	*E*/*Z*[b]	Unreacted **1a** (%)
1	60	6	73:27	92
2	80	68	70:30	25
3	100	95	61:39	0
4	120	75	57:43	0
5	140	45	50:50	0

[a] All reactions without solvent, 0.2 equiv $Fe(CO)_5$, 15 h.
[b] Determined by ^1H NMR.

Two mechanisms may be responsible for the metal-catalyzed conversion of *N*-allylamides to *N*-prop-1-enylamides. Mechanism suggested by Hubert et al.[17] (Scheme 1) includes hydrido-π-complex **3**. However, hydride transfer to the terminal methylene group should give exclusively (*Z*)-isomer **2′**, which was not observed. Moreover, (*E*)-isomer **2** is normally the major one (Table 1). In the control experiment with (*Z*)-enamide, no *E*/*Z* isomerization took place under the reaction conditions. In addi-

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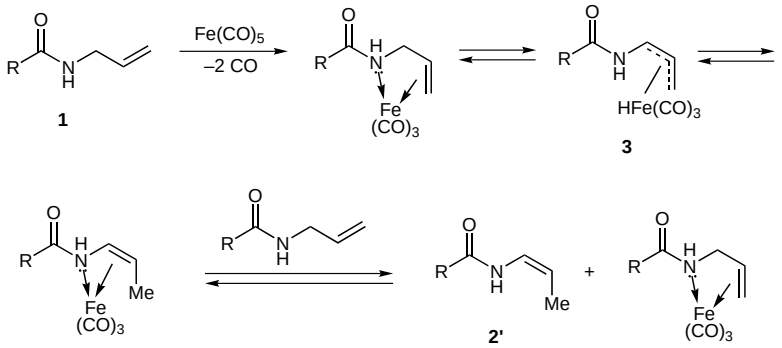
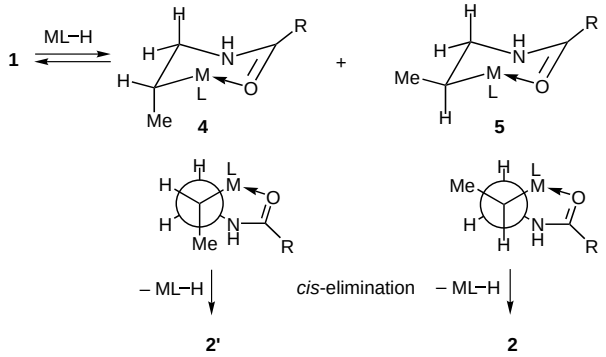


Scheme 1

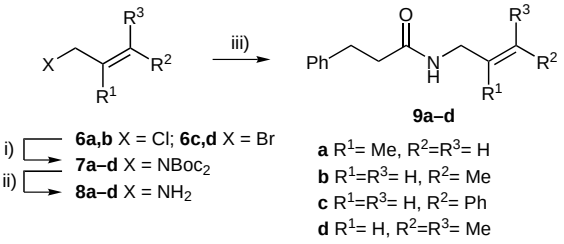
tion, we observed decreasing of *E*/*Z* ratio with raising the temperature (Table 1), indicating that this transformation is kinetically controlled.

Another mechanism was suggested by Stille and Becker[15] for the isomerization of *N*-allylamides upon the action of Ru or Rh hydrides. We assumed, that the similar mechanism occurs in the catalysis with $Fe(CO)_5$. In this case, some iron species like π-complex **3** may be involved as a donor of hydride (Scheme 2). *cis*-Elimination from metallacycle **4** should lead to (*Z*)-enamide **2′**, whereas intermediate **5** gives (*E*)-isomer **2**. Intermediate **4** with a methyl group in the axial position is certainly the less favorable one, therefore the (*Z*)-isomer is the minor reaction product. At elevated temperatures the selectivity of the reaction decreases and both isomers are formed in nearly equal amounts (Table 1).



Scheme 2

Next, we checked the utility of the method for the isomerization of *N*-allylamides containig various functional groups in the acyl residue. Starting *N*-allylamides **1a**–**h** were prepared by acylation of allylamine using standard protocols. Amides **9a**–**d**, bearing additional substituents in allyl moiety, were synthesized in a three-step sequence starting from the corresponding commercially available allylhalides **6** (Scheme 3). Alkylation of **6** with Boc_2NH[18] in the presence of Cs_2CO_3[19] afforded the *N*,*N*-di-Boc derivatives **7**, which were smoothly and quantitatively hydrolyzed with TFA to the corresponding amines **8**. Acylation



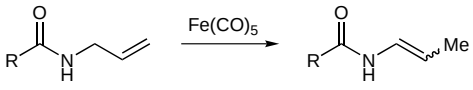
Scheme 3 Reagents and conditions: (i) Boc_2NH, Cs_2CO_3, DMF, r.t., 12 h. (ii) TFA, CH_2Cl_2, r.t., 4 h. (iii) $PhCH_2CH_2COCl$, Et_3N, CH_2Cl_2, 0 °C, 1 h.

of the latter with 3-phenylpropanoyl chloride in the presence of Et_3N delivered the substituted allylamides **9**.[20]

A number of *N*-allylamides was subjected to the isomerization in the presence of $Fe(CO)_5$ (Table 2).[21] Usually, a mixture of (*E*)- and (*Z*)-isomers was obtained, which was in some cases separated by crystallization or column chromatography. Otherwise the *E*/*Z* ratio was determined by ^1H NMR spectroscopy.[22] The double bond in the acyl moiety of crotonoyl amide **1b** underwent no change under the reaction conditions (Table 2, entry 2). The presence of ether or ester groups has no remarkable influence on the migration of the double bond (entries 3, 4). The amino group, protected by Ts or CF_3CO, did not affect the transformation as well (entries 6, 7). In the case of the *N*-Boc group, very widely used in peptide chemistry, the yield was, however, moderate (entry 8). The attempt to perform the isomerization of *N*-(prop-2-enyl)-3-bromopropanamide (**1e**) failed: only recovery of the starting material was observed (entry 5).

Data on isomerization of substituted 3-phenyl-*N*-allylamides **9a**–**d** are summarized in Table 3. Compounds **9a**,**b** demonstrated only partial conversion at 100 °C (entries 1, 3). Hence, further experiments were conducted at 120 °C. Some decomposition of material was observed at this temperature, but the conversion was complete and the yield was still good (entries 2, 4). In the case of the phenylsubstituted allylamide **9c** and the dimethylsubstituted allylamide **9d** the conversion remained incomplete and the yield was relatively low. However, essential amounts of the starting material was recovered and the

Table 2 Isomerization of *N*-Allylamides **1a**–**h** Upon the Action of $Fe(CO)_5$[a]



1a–h **2a–h** (*E*), **2a'–h'** (*Z*)

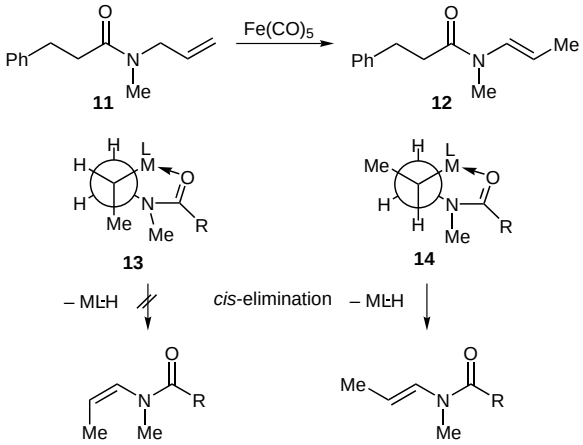
Entry	Starting material	R	Total yield (%)	*E*/*Z*
1	**1a**	$PhCH_2CH_2$	95	61:39[c]
2	**1b**	(*E*)-MeCH=CH	88	71:29[d]
3	**1c**	$MeOCH_2$	72	70:30[c]
4	**1d**	$MeOOC(CH_2)_4$	86	55:45[d]
5	**1e**	$BrCH_2CH_2$	0[f]	–
6	**1f**	$CF_3CONH(Ph)CHCH_2$	89[b,e]	75:25[d]
7	**1g**	TsNH(Ph)CH	90[b]	64:34[d]
8	**1h**	BocNH($PhCH_2$)CH	44[b]	50:50[d]

[a] Reaction without solvent, 0.2 equiv $Fe(CO)_5$, 100°C, 15 h.
[b] Reaction in PhCl.
[c] Products were separated by column chromatography.
[d] Determined by ^1H NMR.
[e] Products were separated by crystallization.
[f] Starting **1e** (71%) was recovered.

yield respective to the reacted material was acceptable (entries 5, 6).[23]

We have shown that the method found could be extended to the tertiary enamides. Isomerization of *N*-methyl-3-phenyl-*N*-(prop-2-enyl)-propanamide **11**[24] afforded the corresponding enamide **12** in good yield. Interestingly, only the (*E*)-isomer was obtained. This is a further argument, supporting the suggested mechanism for migration of double bond. Indeed, intermediate complex **13** is sterically more hindered compared to **4**, which has an H-atom instead of Me group at the N-atom (Scheme 2, Scheme 4). Therefore, difference in energies between **13** and **14** (Scheme 4) is even bigger than between **4** and **5** (Scheme 2).

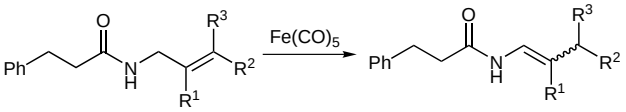
In addition, we demonstrated that by suggested method *N*-allylimides can be converted to *N*-(prop-1-enyl)imides in high yield.[25] Attempts to extend this transformation to *N*-sulfonamides were unsuccessful.[26]



Scheme 4

In summary, we have found a convenient and general method for the conversion of *N*-allylamides to *N*-prop-1-enylamides. The reported procedure has an advantage of inexpensive catalyst and is compatible with various functional groups including protected hydroxy and amino groups. It allows to perform conversion of amides, variously substituted in allyl moiety, with appreciable yields.

Table 3 Isomerization of Substituted *N*-Allylamides **9a**–**d** Upon the Action of $Fe(CO)_5$[a]



9a–d **10a–d** (*E*), **10a'–d'** (*Z*)

Entry	Starting material	Temp (°C)	R^1	R^2	R^3	Yield (%)	*E*/*Z* ratio	Recovery of **9** (%)
1	**9a**	100	Me	H	H	75	–	11
2	**9a**	120	Me	H	H	86	–	0
3	**9b**	100	H	Me	H	63	69:31	30
4	**9b**	120	H	Me	H	59	74:26	0
5	**9c**	120	H	Ph	H	28 (58)[b]	68:32	52
6	**9d**	120	H	Me	Me	22 (76)[b]	83:17	71

[a] All reactions without solvent, 0.2 equiv $Fe(CO)_5$, 15 h.
[b] Yields respective to the reacted **9** are given in parenthesis.

This approach, obviously, provides also a competitive alternative to the known methods for the preparation of tertiary enamides. In addition, it can be of value as a method for removal of *N*-allyl protecting group from amides (isomerization to enamide followed by acidic hydrolysis).

Acknowledgement

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(19) We have shown that the use of Cs_2CO_3 as the phase-transfer catalyst allows to avoid the preparation of Na or K salt of Boc_2NH, see ref.[18a]
(20) **Preparation of *N*-(2-Methylprop-2-enyl)-3-phenylpropanamide 9a (Typical Procedure for the Preparation of Substituted *N*-Allylamides 9a–d).** A mixture of **6a** (4.0 mL, 40 mmol), Boc_2NH (4.34 g, 20 mmol), Cs_2CO_3 (6.52 g, 20 mmol), and DMF (20 mL) was stirred for 12 h at r.t., then the volatile materials were removed in vacuo. The residue was partitioned between CH_2Cl_2 (75 mL) and H_2O (50 mL), the organic phase was separated and washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated to afford crude **7a**. It was dissolved in CH_2Cl_2 (20 mL) and treated with TFA (6.1 mL, 80 mmol) in one portion. After 4 h stirring at r.t. the mixture was concentrated and the residue was dried in vacuo to give crude **8a** as TFA salt. It was dissolved in the mixture of CH_2Cl_2 (75 mL) and Et_3N (8.3 mL, 60 mmol) and treated dropwise at 0 °C with 3-phenylpropanoyl chloride (2.83 mL, 19 mmol). The mixture was stirred for 1 h at 0 °C, then allowed to reach r.t., washed with H_2O (25 mL), 10% aq citric acid (25 mL), again H_2O (2 × 25 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo and crystallization of the residue from hexane/EtOAc afforded **9a** (3.82 g, 94% total yield after 3 steps). Slightly yellow solid, mp 51–52 °C.
^{1}H NMR ($CDCl_3$): δ = 1.65 (s, 3 H, Me), 2.51 (t, 2 H, *J* = 7.7 Hz, CH_2CO), 2.96 (t, 2 H, *J* = 7.7 Hz, C*H*$_2$Ph), 3.75 (d, 2 H, *J* = 6.0 Hz, CH_2N), 4.68, 4.76 (2 s-like m, 2 H, CH_2=C), 5.80 (br s, NH), 7.15–7.28 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$): δ = 20.1 (Me), 31.6 (*C*H_2Ph), 38.3 (*C*H_2CO), 44.9 (CH_2N), 110.7 (*C*H_2=C), 126.1 (arom. CH), 128.2 (2 arom. CH), 128.4 (2 arom. CH), 140.7 (C), 141.8 (C), 172.0 (C=O). CI-MS (NH_3): *m/z* (%) = 407(29) [2 M + 1]$^+$, 221(25) [M + NH_4]$^+$, 204(100) [2 M + 1]$^+$.
(21) **Preparation of 2a/2a′ (Typical Procedure for the Isomerization of *N*-Allylamides to *N*-Prop-1-enylamides).** A mixture of **1a** (945 mg, 5 mmol) and $Fe(CO)_5$ (0.2 mL, 1 mmol) was stirred under Ar for 16 h at 100 °C. The mixture was allowed to reach r.t., then the catalyst was removed in vacuo and collected in a trap, cooled by liquid N_2. Content of the trap was treated with 5% alcoholic $FeCl_3$ solution to destroy toxic $Fe(CO)_5$. The residue in the reaction flask was dissolved in $CHCl_3$ and filtered through Celite. Evaporation of the solvent in vacuo and column chromatography of the residue on silica gel (CH_2Cl_2/EtOAc 10:1) afforded **2a** (548 mg, 58%) and **2a′** (350 mg, 37%), total yield of **2a**/**2a′** 95%.
(*E*)-3-Phenyl-*N*-prop-1-enyl-propanamide(2a). Colorless solid, mp 113–114.5 °C.
^{1}H NMR ($CDCl_3$): δ = 1.62 (dd, 3 H, *J* = 1.7, 6.7 Hz, Me), 2.49 (t, 2 H, *J* = 7.8 Hz, CH_2CO), 2.95 (t, 2 H, *J* = 7.8 Hz, C*H*$_2$Ph), 5.09 (qd, 1 H, *J* = 6.7, 14.2 Hz, C*H*=CHN), 6.71–6.78 (m, 1 H, CH=C*H*N), 7.15–7.28 (m, 5 H, Ph), 7.40 (br d, NH). ^{13}C NMR ($CDCl_3$): δ = 14.7 (Me), 31.4 (*C*H_2Ph), 38.1 (*C*H_2CO), 107.8 (*C*H=CHN), 123.1 (CH=*C*HN), 126.2 (arom. CH), 128.2 (2 arom. CH), 128.4 (2 arom. CH), 140.6 (arom. C), 169.2 (C=O). CI-MS (NH_3): *m/z* (%) = 207(37)[M + NH_4]$^+$), 190(100) [M + 1]$^+$).
(*Z*)-3-Phenyl-*N*-prop-1-enyl-propanamide (2a′). Colorless solid, mp 53.5–55 °C.
^{1}H NMR ($CDCl_3$): δ = 1.49 (dd, 3 H, *J* = 1.5, 7.0 Hz, Me), 2.57 (t, 2 H, *J* = 7.7 Hz, CH_2CO), 2.96 (t, 2 H, *J* = 7.7 Hz, C*H*$_2$Ph), 4.73 (qd, 1 H, *J* = 7.0, 8.9 Hz, C*H*=CHN), 6.64–6.71 (m, 1 H, CH=C*H*N), 7.16–7.28 (m, 6 H, Ph, NH). ^{13}C NMR ($CDCl_3$): δ = 10.7 (Me), 31.4 (*C*H_2Ph), 38.0 (*C*H_2CO), 105.3 (*C*H=CHN), 121.8 (CH=*C*HN), 126.2 (arom. CH), 128.2 (2 arom. CH), 128.5 (2 arom. CH), 140.5 (arom. C), 169.5 (C=O). CI-MS (NH_3): *m/z* (%) = 207(48) [M + NH_4]$^+$, 190(100) [M + 1]$^+$).
(22) *E*/*Z* ratio was determined from the integral intensities of the signals of C*H*=CHN, (*E*)- or (*Z*)-configuration of double bond was assigned based on the value of coupling constants (typically 13.5–14.2 Hz for (*E*)- and 8.5–9.0 Hz for (*Z*)-enamides).
(23) It should be noted, that our findings are in contrast with those of Stille and Becker, reported decomposition of *N*-(3,3-

dimethylallyl)acetamide upon the action of $Fe(CO)_5$, see ref.[15]

(24) Prepared by alkylation of **1a** with MeI in DMF in the presence of NaH.

(25) *N*-Allylphthalimide afforded *N*-(prop-1-enyl)-phthalimide (*E*/*Z* 10: 1) in 99% yield after 15 h at 100 °C. Interestingly, our results were in disagreement with those of Rossi and Barola, reporting only partial conversion of some *N*-allylimides with $Fe(CO)_5$: Rossi, P.; Barola, P. F. *Ann. Chim.* **1969**, *59*, 762.

(26) *N*-Tosylallylamine remained unchanged upon the action of $Fe(CO)_5$.