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Facile Preparation of *N*-Vinylisobutyramide and *N*-Vinyl-2-pyrrolidinone

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Supporting Information

ABSTRACT: A facile synthesis of *N*-vinylakylamides from commercially available *N*-vinylformamide and corresponding acyl chlorides was developed and exemplified by the preparation of *N*-vinylisobutyramide (NVIBA) and *N*-vinyl-2-pyrrolidinone (NVP) in high yields (80−89%). Both NVIBA and NVP are valuable monomers for water-soluble polymers with an array of applications in personal care, pharmaceutical, agricultural, and industrial products.

INTRODUCTION

N-Vinylalkylamides are important monomers to *N*-vinylalkylamide-based homopolymers and copolymers with a broad range of applications of commercial significance. As an example, poly(*N*-vinyl-2-pyrrolidinone) (PVP) is widely used in personal care, pharmaceutical, agricultural, and industrial products.[1] Moreover, some water-soluble *N*-vinylalkylamide-based polymers exhibit dramatic thermoresponsive properties[2] that are of particular interest for potential biomedical applications, including controlled drug delivery, regulating enzyme activity, bioseparations, filtration, and smart surfaces.[3] Among thermoresponsive poly(*N*-vinylalkylamides), poly(*N*-vinylisobutyramide) (PNVIBA), a structural isomer of the conventional thermoresponsive polymer poly(*N*-isopropylacrylamide) (PNIPAM),[4] exhibits a sharp lower critical solution temperature (LCST) of 39 °C[2a] (Figure 1), a potentially valuable property for medical and biotechnological applications.

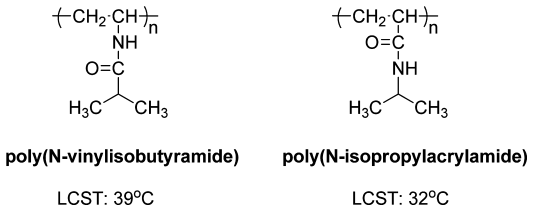
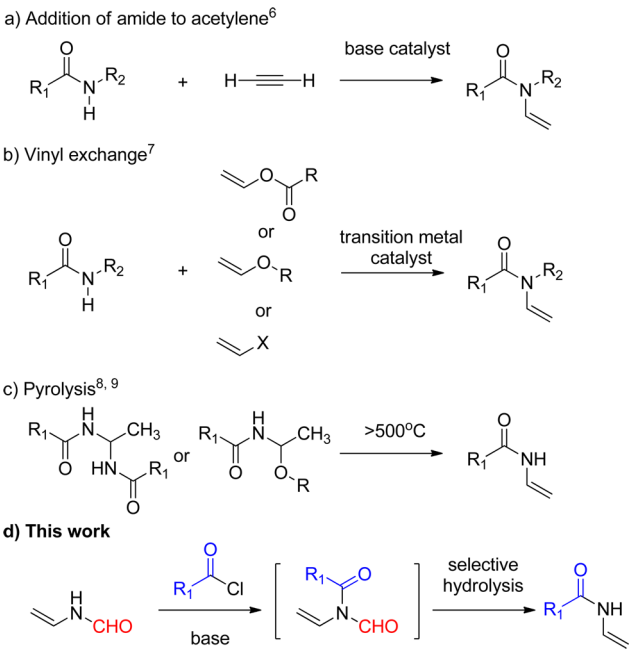


Figure 1. Chemical structures of the repeat units of poly(*N*-vinylisobutyramide) (PNVIBA) and poly(*N*-isopropylacrylamide) (PNIPAM).

Nevertheless, much less attention has been given to PNVIBA and other *N*-vinylalkylamide-based thermoresponsive polymers. The overwhelming majority of studies of thermoresponsive materials are based on PNIPAM. This could be partially due to the limited accessibility to *N*-vinylalkylamide monomers.[5] *N*-Vinylamides are generally prepared by addition of amide to acetylene,[6] vinyl exchange,[7] or pyrolysis of ethylidenebisamide[8] or *N*-(α-methoxyethyl)alkylamide.[9,10] However, these general methods typically suffer from a limited substrate scope and unsatisfactory yields (Scheme 1, paths a−c). Here, we describe a facile one-pot preparation of *N*-vinylalkylamide monomers from commercially available *N*-vinylformamide. The process

Scheme 1. Synthetic Routes to *N*-Vinylalkylamide



involves a simple *N*-acylation of *N*-vinylformamide and subsequent selective removal of the formyl group (Scheme 1, path d). Two valuable monomers, *N*-vinylisobutyramide and *N*-vinyl-2-pyrrolidinone, are conveniently prepared in good yields.

RESULTS AND DISCUSSION

***N*-Vinylisobutyramide.** Our research program required a substantial quantity of *N*-vinylisobutyramide (NVIBA) for preparation of water-soluble polymers. Akashi et al. reported a preparation of NVIBA by pyrolysis of (*N*-α-isopropoxyethyl)-isobutyramide, which was obtained from the reaction of isobutyramide with isopropanol and acetaldehyde in the presence of conc. sulfuric acid. The pyrolysis of (*N*-α-

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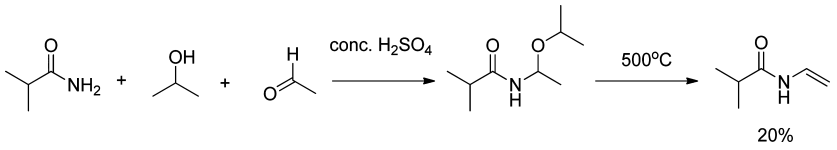
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 2. Akashi's Synthesis of *N*-Vinylisobutyramide (NVIBA)[2a]



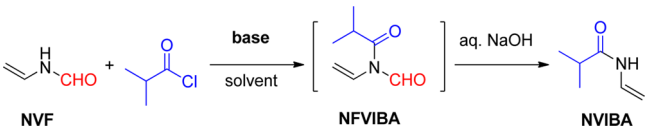
isopropoxyethyl)isobutyramide was conducted at 500 °C under reduced pressure with only 20% yield (Scheme 2).[2a] A convenient and high yielding preparation was desired.

The formyl group of an *N*-formyl-*N*-acyl imide is known to be more susceptible to an acid or base than other acyl groups and can be selectively cleaved to render an amide.[11] *N*-Formyl-*N*-acyl imide can be prepared by *N*-acylation of a formamide with an acyl chloride or a carboxylic anhydride in the presence of a base.[11,12] We were interested to examine such a conventional transformation to prepare NVIBA: converting *N*-vinylformamide (NVF) to the corresponding *N*-vinyl-*N*-formylisobutyramide (NVFIBA), followed by selective removal of the formyl moiety. This conventional strategy avoids harsh and low yielding pyrolysis or costly transition metal catalyzed vinyl exchange reactions and takes advantage of the commercial availability of NVF, a versatile monomer produced by BASF and others in tonne quantities.[13]

We first examined the preparation of NVFIBA by *N*-acylation of *N*-vinylformamide (NVF). Treatment of NVF with isobutyryl chloride using potassium carbonate (K_2CO_3) as the base in acetonitrile (CH_3CN) gave the desired imideNVFIBA and a substantial amount of NVIBA, as indicated by GC-MS analysis of the reaction mixture. The ratio of imide NVFIBA to amide NVIBA was NVFIBA/NVIBA = 1.0:1.5 (noncalibrated GC area ratio). The formation of amide NVIBA indicated that the formyl group of imide NVFIBA was susceptible under the reaction conditions. Thus, instead of an attempt to isolate imide NVFIBA, the resulting mixture was subjected to hydrolysis by addition of an aqueous sodium hydroxide (NaOH) solution, which afforded the desired NVIBA in 65% isolated yield. Encouraged by this result, we next examined use of other bases for the *N*-acylation of NVF to improve the yield of NVIBA. When a solution of potassium *t*-butoxide (KO*t*Bu) in tetrahydrofuran (THF) was used as the base, the reaction of NVF and isobutyryl chloride in THF gave predominantly NVIBA. Only a trace amount of imide NVFIBA was detected by GC-MS. NVIBA was isolated in a higher yield (73%) after subsequent hydrolysis of the reaction mixture with NaOH. When triethylamine (Et_3N) was used as the base, the reaction of NVF and isobutyryl chloride proceeded smoothly to give imide NVFIBA, along with a small amount of NVIBA, in a NVFIBA/NVIBA ratio of 16:1 (by GC analysis). Subsequent hydrolysis of this reaction mixture with aqueous NaOH afforded desired NVIBA in 89% isolated yield (Table 1). By switching the base from K_2CO_3 to Et_3N, the yield of NVIBA was improved from 65 to 89%. A larger preparation of NVIBA using 106.62 g (1.500 mol, 1 equiv) of NVF, 183.80 g (1.725 mol, 1.15 equiv) of isobutyryl chloride, 182.14 g (1.800 mol, 1.20 equiv) of Et_3N, and 900.0 mL (4.500 mol, 3.00 equiv) of 5 N NaOH gave 157.40 g (93%) of NVIBA in 98% purity (by GC analysis). This provided a simple and efficient process for the preparation of NVIBA in high yields under mild conditions.

We also briefly examined the application of this simple method to prepare other *N*-vinyl compounds. *N*-Vinylbenzylamide[14] and isobutyl *N*-vinylcarbamate were similarly

Table 1. Preparation of *N*-Vinylisobutyramide[a]

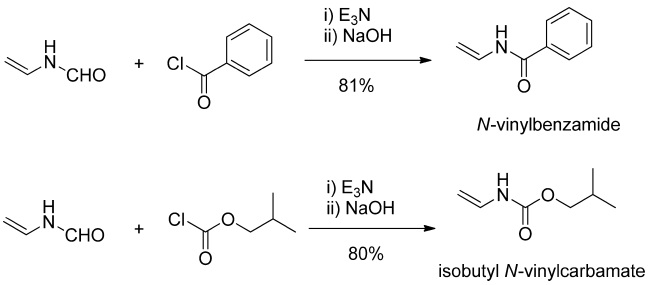


entry	solvent	base	NVIBA (%)[b]
1	CH_3CN	K_2CO_3	65
2	THF	KO*t*Bu	73
3	THF	Et_3N	89

[a]Reactions were carried out using 1 equiv of NVF (100−200 mmol scales), 1.1−1.2 equiv of isobutyryl chloride, and 1.2 equiv of base at 0 °C to room temperature. [b]Isolated yield.

prepared in high yields (Scheme 3),[15] which showed that this methodology is also applicable for the preparation of *N*-vinylarylamide and *N*-vinylcarbamate.

Scheme 3. Preparation of *N*-Vinylbenzamide and Isobutyl *N*-Vinylcarbamate[15]



***N*-Vinyl-2-pyrrolidinone.** *N*-Vinyl-2-pyrrolidinone (NVP) is considered to be the most valuable *N*-vinylamide monomer in terms of significant commercial importance of PVP and other NVP-based polymers, which have been widely used in personal care, pharmaceutical, agricultural, and industrial products.[1] The development of new routes to NVP has been continued since its first production at the beginning of World War II in Germany, and numerous routes have been reported.[16] We were interested in examining the synthesis of NVP from *N*-vinylformamide (NVF) and 4-chlorobutyryl chloride, utilizing the *N*-acylation−deformylation strategy described above. We hypothesize that the hydrolysis of formyl group should lead to the intramolecular cyclization to form NVP (Scheme 4).

Treatment of *N*-vinyformamide (NVF) with 4-chlorobutyryl chloride in the presence of Et_3N as base, however, resulted in a sluggish reaction with multiple byproducts. Subsequent hydrolysis with aqueous NaOH gave a low yield of NVP (30% by GC analysis). Use of NaO*t*Bu as the base also resulted in a complicated reaction, with less than 30% (by GC analysis) of the desired product. This issue was successfully addressed by use of a catalytic amount of 4-dimethylaminopyrridine (DMAP)[17] in combination with Et_3N as the base system, which resulted in a clean reaction, leading to the formation of 98% (by GC analysis) of *N*-formyl-*N*-vinyl-4-chlorobutyryla-

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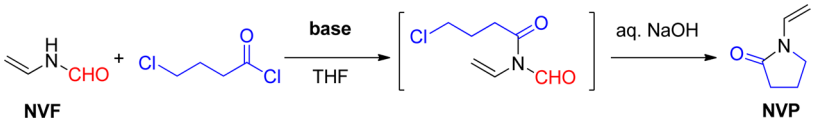
Scheme 4. Alternative Preparation of *N*-Vinyl-2-pyrrolidinone



mide and 2% (by GC analysis) of NVP. Subsequent treatment of the reaction mixture with a solution of 50 wt % NaOH (3.5 equiv relevant to NVF) at 0−5 °C proceeded smoothly to give the desired cyclization product NVP in 80% isolated yield. It was noteworthy that the synthesis was also performed in a one-pot fashion without the need for separation and isolation of intermediate imide *N*-vinyl-*N*-formyl-4-chlorobutyramide. This convenient synthesis provided a facile alternative route to *N*-vinyl-2-pyrrolidinone.

CONCLUSIONS

We have developed a facile one-pot synthesis of NVIBA, a valuable monomer for water-soluble thermoresponsive polymers, by taking advantage of a convenient *N*-acylation of commercially available, inexpensive *N*-vinylformamide and easy removal of the formyl moiety under mild conditions. *N*-Acylation of *N*-vinylformamide with isobutyric chloride in the presence of a base (KO*t*Bu, K_2CO_3, or Et_3N) gave imide NVFIBA, which without separation and isolation was selectively hydrolyzed with aqueous NaOH to produce *N*-vinylisobutyramide in 65 to 89% isolated yields. This provides convenient and efficient synthesis of *N*-vinylalkylamides. Moreover, this strategy was successfully applied to the synthesis of *N*-vinyl-2-pyrrolidinone, the most applicable *N*-vinylamide monomer, from *N*-vinylformamide and 4-chlorobutyryl chloride in a good yield (80%), leading to a facile alternative approach to *N*-vinyl-2-pyrrolidinone.

EXPERIMENTAL SECTION

Solvents and common reagents were purchased from either Fisher or Sigma-Aldrich and were used as received unless otherwise noted. *N*-Vinylformamide, isobutyryl chloride, and 4-chlorobutyryl chloride were purchased from Sigma-Aldrich and distilled prior to use. All reactions were performed under an atmosphere of nitrogen and were monitored by thin-layer chromatography (TLC) and/or gas chromatography (GC)-mass spectra (MS). GC samples were analyzed on an Agilent Technologies 6890 GS system using a J&W DB-5 capillary column. Mass spectra data was obtained using an Agilent Technologies inert mass selective detector (70 eV, EI). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-400 (FT 400 MHz, ^{1}H; 101 MHz, ^{13}C) instrument. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (2) coupling constant (J) quoted in hertz to the nearest 0.1 Hz, and (3) the number of equivalent nuclei (by integration).

Preparation of *N*-Vinylisobutyamide. *Use of Potassium Carbonate (K_2CO_3) as the Base.* In a 500 mL three-necked round-bottomed flask equipped with a stirrer, an addition funnel, and a nitrogen pad was placed anhydrous K_2CO_3 powder (41.46 g, 300.0 mmol), freshly distilled *N*-vinylformamide (14.22 g, 200.0 mmol), and anhydrous acetonitrile (150 mL), and it was cooled with an ice water bath. Freshly distilled isobutyryl chloride (23.44 g, 220.0 mmol) in the addition funnel was added at a rate such that the temperature was maintained at 15−20 °C (30 min). The resulting mixture was stirred overnight at ambient temperature (20−25 °C, 18 h). A drop of the reaction mixture was taken and diluted with EtOAc (2 mL), and insolubles were filtered off. The aliquot was then analyzed by GC-MS, which showed the presence of both NVFIBA and NVIBA in a ratio of NVFIBA/NVIBA = 1.0:1.5 (noncalibrated GC area ratio). Water (120 mL) was added to the reaction mixture to dissolve all of the solids, followed by addition of 50 wt % NaOH (22.20 g, 278.0 mmol). The mixture was stirred at ambient temperature until the imide intermediate NVFIBA disappeared, as monitored by GC. The water layer was removed and extracted with methylene chloride (CH_2Cl_2, 100 mL × 2). The organic layers were combined and washed with a solution of sat. NaCl (100 mL). The solvents were evaporated using rotary evaporation under reduced pressure. The residual oil was subjected to distillation under reduced pressure to give the desired NVIBA (14.81 g, 65% yield) as a colorless oil (bp 70−72 °C/1 mmHg), which solidified at room temperature (mp 58−59 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (b, 1H), 7.09 (dd, J_1 = 16.0 Hz, J_2 = 8.8 Hz, 1H), 4.60 (d, J = 16.0 Hz, 1H), 4.40 (d, J = 8.8 Hz, 1H), 2.11 (sept, J = 7.2 Hz, 2H), 1.19 (d, J = 7.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 128.8, 94.9, 35.6, 19.3.

Use of Potassium t-Butoxide (KOtBu) as the Base. In a 500 mL three-necked round-bottomed flask equipped with a stirrer, an addition funnel, and a nitrogen pad was placed a solution of 1 N KO*t*Bu in THF (250.0 mL, 250.0 mmol), and it was cooled to 10 °C with an ice-water bath. Freshly distilled *N*-vinylformamide (14.22 g, 200.0 mmol) in the addition funnel was added at a rate such that the temperature was maintained below 20 °C. The resulting mixture was stirred at 15−20 °C for 1 h. Then, freshly distilled isobutyryl chloride (23.44 g, 220.0 mmol) was added at 15−20 °C (30 min). The resulting mixture was stirred overnight at ambient temperature (18 h). A drop of the reaction mixture was taken and diluted with EtOAc (2 mL), and the insolubles were filtered off. The aliquot was then analyzed by GC-MS, which showed that NVIBA was the major product, along with only a trace amount of imide NVFIBA. Thus, the reaction was quenched by addition of 50 wt % NaOH (20.00 g, 250.0 mmol) and water (50 mL) at 15 °C. After stirring for 4 h at ambient temperature, the mixture was set for phase separation. The water layer was removed and extracted with methylene chloride (CH_2Cl_2, 100 mL × 2). The organic layers were combined and washed with a solution of sat. NaCl (100 mL). The solvents were evaporated using rotary evaporation under reduced pressure. The residual oil was distilled under reduced pressure to give the desired NVIBA (16.41 g, 73% yield) as a colorless oil (70−75 °C/mmHg), which solidified at room temperature (mp 58−59 °C). The ^{1}H and ^{13}C NMR spectra were consistent with those from the compound synthesized above.

Use of Triethylamine as the Base. Freshly distilled *N*-vinylformamide (14.22 g, 200.0 mmol), triethylamine (24.29 g, 240.0 mmol), and anhydrous THF (150 mL) were added to a

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Org. Process Res. Dev. XXXX, XXX, XXX−XXX

500 mL three-necked round-bottomed flask equipped with a magnetic stirrer, a thermometer, and a nitrogen pad. The resulting mixture was cooled to 0 °C in an ice-water bath. Freshly distilled isobutyryl chloride (24.51 g, 230.0 mmol) was slowly added through a syringe pump at a rate such that the temperature was maintained below 5 °C over 30 min. The resulting reaction mixture was stirred at 0−5 °C for 2 h. A drop of the reaction mixture was taken and diluted with EtOAc (2 mL), and the insolubles were filtered off. The aliquot was then analyzed by GC-MS, which showed that the reaction was complete, resulting in mainly NFVIBA and a small amount of NVIBA, in a ratio of NVFIBA/NVIBA = 16:1 (by GC analysis). A solution of 5 N NaOH (120 mL, 600.0 mmol) was then slowly added at 0−5 °C over 2 h. The resulting thick mixture was stirred at 0−5 °C until all of the imide NVFIBA disappeared, as monitored by GC (1−2 h). The water layer was removed and extracted with EtOAc (100 mL × 2). The organic layers were combined and washed with a solution of sat. NaCl (150 mL). The solvents were evaporated under reduced pressure using rotary evaporation. The residual oil was purified by distillation to give NVIBA (20.14 g, 89% yield) as a colorless oil, which solidified at room temperature. The ^{1}H and ^{13}C NMR spectra were consistent with those from the compound synthesized above.

A Larger Preparation of N-Vinylisobutyramide. Freshly distilled *N*-vinylformamide (106.62 g, 1.500 mol), triethylamine (182.14 g, 1.800 mol), and anhydrous THF (1.0 L) were added to a 3 L four-necked round-bottomed flask equipped with an overhead stirrer, an addition funnel, a thermometer, and a nitrogen pad. The resulting mixture was cooled to 0 °C in an ice-water bath. Freshly distilled isobutyryl chloride (106.55 g, 1.725 mol) was loaded into the addition funnel and slowly added at a rate such that the temperature was maintained below 5 °C over 1 h. The resulting reaction mixture was stirred at 0−5 °C until the reaction was complete, as monitored by GC analysis (2 h). A solution of 5 N NaOH (900.0 mL, 4.500 mol) was then slowly added at 0−5 °C over 2 h. The resulting thick mixture was stirred at 0−5 °C until all of the imide NVFIBA disappeared, as monitored by GC (1−2 h). The water layer was removed and extracted with EtOAc (500 mL × 2). The organic layers were combined, washed with a solution of sat. NaCl (500 mL × 2), and dried over anhydrous sodium sulfate. After filtering off insolubles, the solvents were evaporated under reduced pressure using rotary evaporation to give a slightly brown solid. The solid was further dried in a vacuum oven at 1 mmHg/25 °C to a constant weight to give 157.40 g (93% yield) of the desired product in 98% purity (estimated by GC analysis).

Preparation of *N*-Vinyl-2-pyrrolidinone. Freshly distilled *N*-vinylformamide (NVF, 7.11 g, 100.0 mmol), triethylamine (14.17 g, 140.0 mmol), 4-dimethylaminopyridine (DMAP, 0.61 g, 5 mol %), and anhydrous THF (80 mL) were added to a 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer, a thermometer, and a nitrogen pad. The mixture was cooled to 0 °C with an ice-water bath. 4-Chlorobutyryl chloride (16.92 g, 120.0 mmol) was added through a syringe pump at a rate (28 mL/h) such that the temperature was maintained at 0−5 °C over 30 min. The reaction mixture was stirred at 0−5 °C for 1 h. A sample was taken and analyzed by GC, which showed that the conversion was complete, giving 98% (by GC analysis) *N*-formyl-*N*-vinyl-4-chlorobutylamide along with 2% (by GC analysis) cyclization product NVP. A solution of 50 wt % NaOH (28.0 g, 350.0 mmol) was then added through a syringe pump at 0−5 °C over 30 min. The resulting mixture was stirred for 1 h. A sample was taken and analyzed by GC-MS, which showed the formation of 95% (by GC analysis) NVP and 5% (by GC analysis) impurities. DI water (50 mL) was added to dissolve the solid. The water layer was removed and extracted with EtOAc (100 mL × 2). The organic layers were combined and washed with sat. NaCl (150 mL). The solvents were evaporated under reduced pressure by rotary evaporation. The residue was distilled at 82 °C/4 mmHg to afford NVP (8.82 g, 80% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, J_1 = 16 Hz, J_2 = 8 Hz, 1H), 4.45 (d, J = 8 Hz, 1H), 4.41 (d, J = 16 Hz, 1H), 3.52 (t, J = 8 Hz, 2H), 2.50 (t, J = 8 Hz, 2H), 2.11 (qt, J = 8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 129.3, 94.2, 44.5, 31.3, 17.3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00303.

Spectral information for *N*-vinylisobutyramide, *N*-formyl-*N*-vinyl-4-chlorobutyramide, and *N*-vinyl-2-pyrrolidinone (PDF)

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Notes

The authors declare no competing financial interest.

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(15) (a) *N*-Vinylbenzamide was obtained in 81% yield in the presence of 5 mol % DMAP as catalyst. Without DMAP, the isolated yield was 52%. The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[14] (b) Reaction of *N*-vinylformamide and isobutyl chloroformate in the presence of Et_3N as the base in THF gave isobutyl *N*-formyl-*N*-vinylcarbamate, which, without isolation, was subsequently hydrolyzed with 5 N NaOH to give isobutyl *N*-vinylcarbamate in 80% isolated yield. ^{1}H NMR (400 HMz, $CDCl_3$) δ 6.70 (m, 1H), 6.39 (s, 1H), 4.47 (d, J = 15.2 Hz, 1H), 4.27 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 6.4 Hz, 2H), 1.94 (m, 1H), 0.94 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 HMz, $CDCl_3$) δ 153.8, 130.0, 92.8, 71.2, 19.0. HRMS calcd for $C_7H_{13}NO_2$ (M^+), 143.0941; found, 143.0945.
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