Enol Formates: Ruthenium Catalysed Formation and Formylating Reagents

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The one-step synthesis of the enol formates, isopropenyl,hex-1-en-2-yl, and α-methylenebenzyl formates, directly from terminal alkynes and formic acid with arene–ruthenium(II) catalysts is reported. They have been shown to be effective formylating reagents, under mild and neutral conditions, to produce formamides from primary and secondary amines, formylamino esters, and in the presence of a catalytic amount of imidazole, formates from alcohols or phenols.

Formyl compounds, useful synthetic intermediates in oxidations, reductions and homologations, have been widely used for the protection of amino or hydroxy groups. For example, a number of amino acids have been synthesised after protection of the amino functionality by a formyl group, which can be easily cleaved under acidic conditions.[1] The key step in the synthesis of benzomorphans by enantioselective hydrogenation of a *Z*-enamine is due to the presence of a formyl group that assists and orientates the reaction catalysed by chiral ruthenium complexes.[2] *N*-Formylamides, the starting material of choice for preparation of isocyanides by dehydration with phosgene, phosphorus oxychloride[3] or phosphorus pentoxide,[4] have been used to prepare biologically active substances such as vitamin B6 (pyridoxin) from *N*-formyl-D,L-alanine ethyl ester,[4] antibiotics,[5] and for the synthesis of polypeptides by the four component method.[6] Some *N*-formylpeptides themselves show biological activity as chemoattractants.[7]

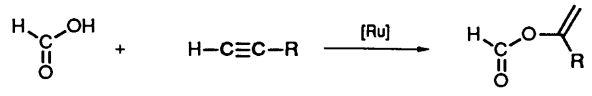
Many *N*- and *O*-formylation methods are known, but simple reactions with acyl halides or anhydrides are difficult to carry out, since formyl halides and formic anhydride are not stable. For this reason, most formylating agents are reactive formyl derivatives generated *in situ*. *N*-Formyl derivatives have been used for the *N*-formylation of amines, amides and imines, including *N*,*N*-diformylacetamide,[8] *N*-formylimidazole and 4-formyl-2-methyl-1,3,4-thiadiazolin-5-one.[9] However all these methods produce undesirable by-products. Formic acid itself can formylate alcohols[10] and amines,[11] but its methyl or phenyl ester and mixed anhydrides such as acetic formic[9] or pivalic formic anhydride,[2] are more conveniently used. Formyl fluoride prepared from formic acid and cyanuric fluoride[12] is a very efficient agent which allows the formylation of amines, alcohols, phenols and thiols at 0 °C, in the presence of tertiary amines,[13] but it has to be prepared just before use because of its instability.

Interestingly, van Melick and co-workers reported that isopropenyl formate was able to formylate amines under neutral conditions.[14] This method was dependent on the formation of the isopropenyl formate by a multi-step synthesis (overall yield of *ca.* 50%) starting from alkyl orthoformate, 1-chloropropan-2-ol and chloroacetic acid.[15]

We have previously reported that some enol esters were available in one step, from carboxylic acids and terminal alkynes in the presence of ruthenium–phosphine complexes.[16] Other additions of carboxylic acids to alkynes have been performed using $[Ru(C_8H_{11})_2]$ as catalyst precursor.[17] We now report the catalytic synthesis of isopropenyl **1a**, hex-1-en-2-yl **1b**, and α-methylenebenzyl **1c** formates, directly from formic acid with arene–ruthenium(II) catalysts, and the use of **1a** and **1b** as formylating reagents for amines, amino esters and alcohols under mild conditions.

Results and Discussion

Ruthenium Catalysed Addition of Formic Acid to Terminal Alkynes.—In the presence of a catalytic amount of a ruthenium complex, the regioselective addition of formic acid to terminal alkynes afforded the enol formates **1a–c** in good yields.



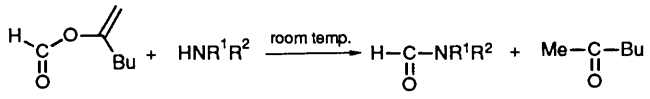
1a - c

R = Me **1a**, Bu **1b**, Ph **1c**
Isolated yields: **1a** (45%), **1b** (78%), **1c** (95%)

The regioselectivity of the reaction was critically dependent on the nature of the ruthenium complex. $RuCl_3 \cdot 3H_2O$ in the presence of 2 equiv. of phosphine, or better $[Ru(arene)(PR_3)Cl_2]$ complexes gave **1a–c** regioselectively whereas $RuCl_3 \cdot 3H_2O$ used without a phosphine gave a mixture of **1a–c**, and *Z*- and *E*-enol formates corresponding to the addition of the carboxylate to the terminal carbon of the alkyne. With $[Ru(p\text{-cymene})(PPh_3)Cl_2]$,[18] these last mentioned isomers could not be detected by GLC and ^1H NMR. The solvents, toluene for **1c**, hexane for **1b** and decalin for **1a** were selected according to the volatility of the enol formate to allow the separation by distillation. Owing to its volatility, **1a** was difficult to isolate pure (45%) but the conversion of the acid was complete since the reaction of the resulting crude isopropenyl formate with morpholine at room temperature afforded a 97% yield of the formamide. All these compounds were characterized spectroscopically and by satisfactory elemental analyses.

Formylation of Amines and Alcohols.—Isopropenyl **1a** and hex-1-en-2-yl **1b** formates gave a very fast and exothermic reaction with simple primary and secondary amines to afford *N*-formamides and neutral ketones. A quantitative reaction of **1b** with aniline, *p*-toluidine, diethylamine, morpholine and hexamethyleneimine, in ethyl acetate at room temp. for 1 h gave the corresponding *N*-formamides **2a–e** in 85, 75, 62, 90 and 76% isolated yield, respectively. To obtain a quantitative overall yield from the volatile isopropenyl formate **1a** there is an advantage in using the crude derivative, as no by-products are formed. It was noteworthy that enol formates were much more reactive than alkyl formates since no amide was obtained when aniline was treated at 50 °C for 72 h with methyl formate. It must also be pointed out that the acylation with secondary amines was not possible under these conditions with other enol esters of aliphatic or aromatic acids such as isopropenyl pivalate or benzoate.[19] The usefulness of acid labile *N*-protecting groups

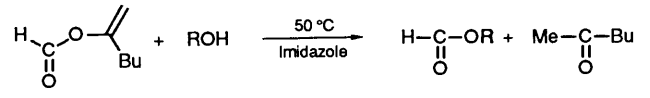
in peptide formation coupled with the fact that this formylation occurs under neutral conditions makes it very appropriate for peptide synthesis. Thus the ethyl esters of glycine, alanine and phenylalanine, liberated from their hydrochlorides with Et_3N were formylated with hex-1-en-2-yl formate in methanol at 20 °C within 1 h to give **2f** (70%), **2g** (74%) and **2h** (71%). These products, **2f–h** are precursors of isocyanides that are key components for the synthesis of peptides according to the Ugi reaction[6] or related methods.[20]



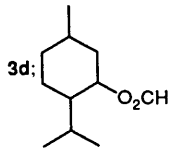
2a - h

2a; HCONHPh
2b; HCONHC$_6$H$_4$Me
2c; HCONEt$_2$
2d; HCON O
2e; HCON(CH$_2$)$_5$CH$_2$
2f; HCONHCH$_2$CO$_2$Et
2g; HCONHCH(Me)CO$_2$Et
2h; HCONHCH(CH$_2$Ph)CO$_2$Et

Although, under similar conditions, primary and secondary alcohols failed to react quickly with enol formates **1a–b**, formylation occurred in the presence of basic catalysts such as imidazole or dimethylaminopyridine (DMAP). Hexanol or prop-2-ynyl alcohol when stirred with hex-1-en-2-yl formate **1b** at 50 °C for 24 h in tetrahydrofuran (THF), in the presence of a catalytic amount of imidazole (10%), gave the corresponding esters **3a–b**. Similarly, benzyl formate **3c** (60%) and menthyl formate **3d** (70%) were obtained from benzyl alcohol and menthol after 24 and 48 h respectively. From *p*-cresol and **1b** in the presence of imidazole at 40 °C in acetonitrile formation of the ester **3e** was shown to be at an optimum after 30 h (73% yield in *p*-tolyl formate **3e** determined by GPC).



3a; HCO$_2$—C$_6$H$_{13}$
3b; HCO$_2$—CH$_2$C≡CH
3c; HCO$_2$—CH$_2$Ph
3e; HCO$_2$—C$_6$H$_4$Me
3d;



Experimental

Synthesis of Enol Formates.—Formic acid (20 mmol), the alkyne (25 mmol), the catalyst [Ru(*p*-cymene)(PPh$_3$)Cl$_2$][18] (0.2 mmol), and the solvent (20 cm^3) were stirred under argon for 15 h at 80–100 °C. The enol formates were isolated by distillation under reduced pressure (1–2 mmHg).

Isopropenyl formate **1a**; δ_H(80 MHz; $CDCl_3$) 8.07 (1 H, s, CHO), 4.70 (2 H, s, CH_2=C) and 2.13 (3 H, s, CH_3); ν/cm^{-1} 1750 (C=O) and 1680 (C=C).[15a]

Hex-1-en-2-yl formate **1b**; δ_H(80 MHz; $CDCl_3$) 8.08 (1 H, s, CHO), 4.69 (2 H, s, CH_2=C), 2.20 (2 H, t, *J* 7, OCH_2), 1.40 (4 H, m, 2-CH_2) and 0.90 (3 H, t, *J* 6.5, CH_3); ν/cm^{-1} 1750 (C=O) and 1680 (C=C) (Found: M$^+$, 128.083. $C_7H_{12}O_2$ requires *M*, 128.084).

α-Methylenebenzyl formate **1c**; δ_H(80 MHz; $CDCl_3$) 8.22 (1 H, s, CHO), 7.6–7.25 (5 H, m, Ph), 5.44 (1 H, d, *J* 2.6, CH_2=C) and 4.99 (1 H, d, *J* 2.6, CH_2=C); ν/cm^{-1} 1770 (C=O) and 1650 (C=C) (Found: C, 72.1; H, 5.6%; M$^+$, 148.042. $C_9H_8O_2$ requires C, 72.9; H, 5.45%; *M*, 148.042).

Formylation of Amines.—The amine (10 mmol) was dissolved in ethyl acetate (10 cm^3) and the enol formate (10 mmol) was added at room temp. An exothermic reaction immediately took place and after 1 h the absence of enol formate was shown by GLC. *N*-Formamides **2a** and **2b** were recrystallized from ether–hexane mixtures and formamides **2c–e** were isolated by distillation under reduced pressure. In the case of amino esters, the corresponding hydrochloride (10 mmol) was dissolved in methanol (10 cm^3) in the presence of triethylamine (10 mmol) and enol formate (10 mmol) was added and allowed to react at room temperature for 1 h. The solution was evaporated and the ammonium salt filtered off and washed with ether. *N*-Formyl amino esters were then chromatographed on a silica column using ether as eluent.

Phenylformamide **2a**; δ_H(80 MHz; $CDCl_3$) 8.65 (1 H, s, NH), 8.35 (1 H, s, CHO) and 6.8 (5 H, m, Ph); ν/cm^{-1} 3300 (NH) and 1700 (C=O) (Found: C, 69.4; H, 5.8; N, 11.6%; M$^+$, 121.053. C_7H_7NO requires C, 69.4; H, 5.8; N, 11.6%; *M*, 121.053).

p-Tolylformamide **2b**; δ_H(80 MHz; $CDCl_3$) 8.05 (1 H, s, CHO), 7.1–6.8 (4 H, m, Ph) and 2.2 (3 H, s, CH_3); ν/cm^{-1} 1690 (C=O).

N,N-*Diethylformamide* **2c**; δ_H(80 MHz; $CDCl_3$) 8.03 (1 H, s, CHO), 3.26 (4 H, q, *J* 8, 2-CH_2) and 1.2 (6 H, t, *J* 8, 2-CH_3); ν/cm^{-1} 1690 (C=O) (Found: M$^+$, 101.084. $C_5H_{11}NO$ requires *M*, 101.084).

N-Formylmorpholine **2d**; δ_H(80 MHz; $CDCl_3$) 8.05 (1 H, s, CHO) and 3.25–3.8 (8 H, m, 4-CH_2); ν/cm^{-1} 1690 (C=O).

N-*Formylhexahydroazepine* **2e**; δ_H(80 MHz, $CDCl_3$) 8.06 (1 H, s, CHO), 3.43 (2 H, t, *J* 5.6, CH_2), 3.36 (2 H, t, *J* 5.6. CH_2), 1.6 (8 H, m, 4-CH_2); ν/cm^{-1} 1680 (C=O) (Found: M$^+$, 127.100. $C_7H_{13}NO$ requires *M*, 127.100).

N-Formylglycine ethyl ester **2f**; δ_H(80 MHz; $CDCl_3$) 8.22 (1 H, s, CHO), 7.0 (1 H, br s, NH), 4.1 (2 H, q, *J* 7.1, CH_2), 4.02 (2 H, d, *J* 8, CH_2) and 1.25 (3 H, t, *J* 7.1, CH_3); ν/cm^{-1} 3400 (NH), 1750 (C=O ester) and 1700 (C=O formyl).

N-*Formylalanine ethyl ester* **2g**; δ_H(80 MHz; $CDCl_3$) 8.17 (1 H, s, CHO), 6.84 (1 H, br s, NH), 4.67 (1 H, m, CH), 4.19 (2 H, q, *J* 7.2, CH_2) and 1.45–1.17 (6 H, d + t, *J* 7.2, 2-CH_3); ν/cm^{-1} 3310 (NH), 1742 (C=O ester), 1673 (C=O formyl) (Found: C, 49.4; H, 7.6; N, 9.45%; M$^+$, 145.074. $C_6H_{11}NO_3$ requires C, 49.6; H, 7.6; N, 9.65%; *M*, 145.074).

N-*Formylphenyalanine ethyl ester* **2h**; δ_H(80 MHz; $CDCl_3$) 8.10 (1 H, s, CHO), 7.20 (5 H, m, Ph), 6.30 (1 H, br s, NH), 4.83 (1 H, m, CH), 4.13 (2 H, q, *J* 7.2, CH_2), 3.09 (2 H, d, *J* 6, $PhCH_2$) and 1.19 (3 H, t, *J* 7.2, CH_3); ν/cm^{-1} 3340 (NH), 1739 (C=O ester) and 1686 (C=O formyl) (Found: C, 65.9; H, 7.1; N, 6.6. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%).

Formylation of Alcohols.—Alcohol (10 mmol), imidazole (1 mmol) and enol formate **1b** (10 mmol) were dissolved in THF or acetonitrile (10 cm^3) and stirred until no starting material could be detected by GLC. The solvent was then evaporated and the formyl esters **3c**, **3d** and **3e** were chromatographed over silica gel with an ether–hexane (10:90) mixture. Hexyl formate **3a** and prop-2-ynyl formate **3b** could not be separated from the solvent but were characterized in solution.

Benzyl formate **3c**; δ_H(80 MHz; $CDCl_3$) 8.04 (1 H, s, CHO), 7.4 (5 H, s, Ph) and 4.2 (2 H, s, CH_2); ν/cm^{-1} 1725 (C=O) (Found: C, 69.7; H, 6.4%; M$^+$, 136.052. $C_8H_8O_2$ requires C, 70.6; H, 5.9%; *M*, 136.052).

2-*Isopropyl-5-methylcyclohexyl formate* **3d**; δ_H(300 MHz; $CDCl_3$) 8.04 (1 H, s, CHO), 4.77 (1 H, dt, *J* 4 and 10.6, 1-H), 2 (1 H, dm, *J* 12, 6-H), 1.87 (1 H, d sept, *J* 7 and 29, 8-H), 1.66 (2 H, m, 3-H and 4-H), 1.46 (1 H, m, 5-H), 1.37 (1 H, m, 2-H), 1.1–0.8 (3 H, m, 3-H, 4-H and 6-H), 0.88 (2 × 3 H, 2 × d, *J* 7, 2 × CH_3) and 0.73 (3 H, d, *J* 6.9, CH_3); ν/cm^{-1} 1726 (C=O) (Found: C, 70.7; H, 10.9%. $C_{11}H_{20}O_2$ requires C, 71.7; H, 10.95%).

p-Tolyl formate **3e**; δ_H(80 MHz; $CDCl_3$) 8.22 (1 H, s, CHO), 7.14 (2 × 1 H, d, J_{ab} 8), 6.96 (2 × 1 H, d, J_{AB} 8) and 2.30 (3 H, s, CH_3); ν/cm^{-1} 1736 (C=O).

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