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Copper-promoted iodovinylation of amides: synthesis of β-functionalized enamides

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Abstract

We studied the addition of nitrogen radicals to ynol ethers in order to form β-functionalized enamides. Poor yields are reported. On the other hand, we observed that copper coupling between 1,2-diiodoethene and various amides leads to β-functionalized enamides in high yields with complete stereocontrol.

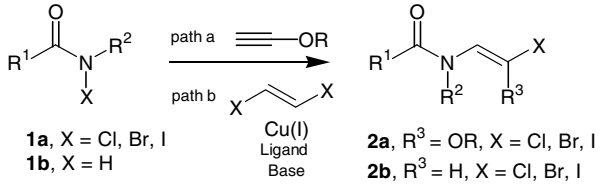
1. Introduction

Enamides are functional groups often encountered in many biologically active natural products as well as drug candidates.[1] Several methods of enamides synthesis have been developed. While α-functionalized enamides are readily prepared,[2] β-functionalized enamides are not synthesized as easily. Their preparation generally requires multistep sequences, often with low yields and/or poor stereoselection.[3]

Herein we report two synthetic avenues to prepare β-functionalized enamides in a straightforward manner.

First, we envisaged the possibility of using radical chemistry. Previous studies have demonstrated that the radical addition of *N*-haloamides to alkenes and enols ethers is an efficient method for simultaneously form C–N and carbon–halogen bonds.[4] This gave us the idea of exploring the addition of nitrogen radicals to ynol ethers (Scheme 1, path a). This methodology would readily produce highly functionalized β-functionalized enamides (**2a**) under mild and neutral conditions.

We also considered an alternate approach for the synthesis of β-functionalized enamides based on copper-catalyzed coupling (Scheme 1, path b). It is known that enamides can be readily prepared using a coupling reaction between amides and vinyl monohalides.[2] However, we could find no examples of copper-catalyzed coupling between amides and vinyl dihalides that would lead to β-functionalized enamides (**2b**). We thus decided to explore this avenue, knowing that we had to take good care of reaction conditions in order to avoid any double substitution.



Scheme 1.

2. Addition of *N*-halo compounds to ynol ethers

To examine the ability of nitrogen radical to add to ynol ether triple bond, we first had to synthesize nitrogen radical precursors. We thus prepared various *N*-halo amides, carbamates, and sulfonamides (see Table 1). Their structure was chosen in order to present different polar and steric effects in the subsequent addition to ynol ethers.

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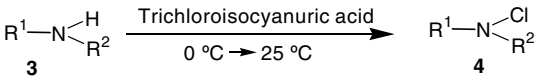
Table 1
N-Chlorination of amides, lactams, carbamates, and sulfonamides



3 **4**

Starting material		Product		Isolated yield (%)
3a	$R^1 = PhSO_2–$, $R^2 = H–$	**4a**	$R^1 = PhSO_2–$, $R^2 = Cl–$	94
3b	$R^1 = PhSO_2–$, $R^2 = Ac–$	**4b**	$R^1 = PhSO_2–$, $R^2 = Ac–$	99
3c	$R^1 = EtO_2C–$, $R^2 = H–$	**4c**	$R^1 = EtO_2C–$, $R^2 = Cl–$	72
3d	$R^1 = Ac–$, $R^2 = Me–$	**4d**	$R^1 = Ac–$, $R^2 = Me–$	95
3e	$R^1, R^2 = –CO(CH_2)_3–$	**4e**	$R^1, R^2 = –CO(CH_2)_3–$	91

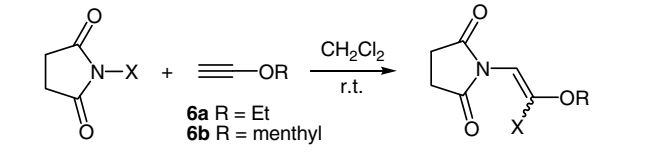
3. Synthesis of *N*-halo amides, carbamates, and sulfonamides

A convenient method for the synthesis of *N*-halo derivatives involves the use of the commercially available trichloroisocyanuric acid (TCCA) as a source of chlorine.[5] The latter is added to the amide and the reaction is performed under very mild conditions at room temperature. Table 1 summarizes our results of the syntheses of various *N*-halo derivatives. To the best of our knowledge, it is the first time that dichlorobenzenesulfonamide (**4a**), *N*-acetyl-*N*-chlorobenzenesulfonamide (**4b**) and dichlorourethane (**4c**) are prepared using this method.

Monochlorourethane, prepared following Lessard's protocol,[6] and *N*-halosuccinimides (**5**, see Scheme 2), commercially available, were also used in the addition study.

4. Reaction of ynol ethers and *N*-halo compounds

The next step was to react these *N*-halo compounds with ynol ethers. We used commercially available ethoxyacetylene as the prototypical substrate. Menthoxypropyne[7] was also used as ynol ether. The reactions were carried out in a variety of solvents including toluene, methylene chloride, methanol, and acetonitrile. However, only methylene chloride allowed us to observe any desired adducts. Several reaction parameters were tested: temperature (−78 °C to rt), addition order and concentration of reactants. Radical chain reaction was initiated either spontaneously or by the addition of triethylborane. The reactions studied were quite sluggish. We regularly obtained a reaction mixture composed of numerous products. Among the reactions investigated, only two showed an interesting adduct/by-products ratio (Scheme 2). NCS and NIS (**5**, X = Cl and I) added to ethoxyacetylene and led to the desired product (**7a** and **7b**) with 35% and 17% yield, respectively. Note that only one stereoisomer was observed (though the exact stereochemistry is yet to be determined).



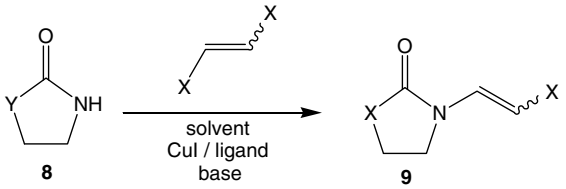
Scheme 2.

5. Copper-catalyzed coupling between amides and 1,2-dihaloethene

The results above show that the radical addition toward ynol ethers is not a viable method for the preparation of β-functionalized enamides. We thus investigated the possibility of producing these entities using a copper coupling procedure.

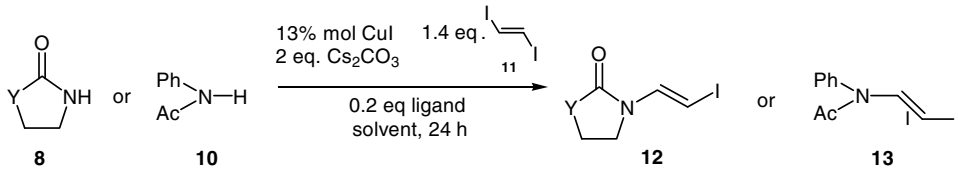
We started our investigation by reacting 1,2-dichloroethene (Scheme 3, X = Cl) with cyclic amides **8a** and **8b** under various copper coupling reaction conditions. These experimental procedures were chosen for their proven efficiency in coupling reactions involving amides.[2a] We tested different temperatures (55 °C, 80 °C, 110 °C), different ligands (*N*,*N*′-dimethyl ethylenediamine (DMEDA), 1,10-phenanthroline, *N*,*N*-dimethylglycine) and different solvents (THF, 1,4-dioxane, and toluene). Unfortunately, no desired compounds were isolated under these various conditions. This result is, however, not surprising considering that it is known that vinyl chlorides generally do not participate in this kind of copper coupling.[8] We then used the commercially available mixture of 1,2-dibromoethene (~2:1 *E*:*Z*) (Scheme 3, X = Br). Again, under the same various conditions, we could not obtain the desired enamides.

Finally, we tested the reaction between the readily available 1,2-diiodoethene[9] (**11**, pure *E*-isomer, see Table 2) and amide **8a**. Happily, the desired enamide **9ac** was isolated with 75% yield. DMEDA turned out to be the best ligand for this reaction (Table 2, compare entry 1 with entries 2–4). Note that none of the disubstituted product was observed. The optimal temperature reaction is 55 °C and the best solvent is THF.



Scheme 3.

Table 2
Copper-catalyzed coupling between amide derivatives and 1,2-diiodoethene



Entry	Starting compound	Temperature (°C)	Solvent	Ligand	Product	Isolated yield (%)
1	**8a** Y = CH_2	55	THF	DMEDA	**12a** Y = CH_2	75
2	**8a** Y = CH_2			1,10-Phenanthroline	**12a** Y = CH_2	66
3	**8a** Y = CH_2			*N*,*N*-Dimethylglycine	**12a** Y = CH_2	74
4	**8a** Y = CH_2			No ligand	**12a** Y = CH_2	40
5	**8a** Y = CH_2	80	Toluene	1,10-Phenanthroline	**12a** Y = CH_2	71
6	**8b** Y = O	55	THF	DMEDA	**12b** Y = O	94
7	**8c** Y = CH_2CH_2	55	THF	DMEDA	**12c** Y = CH_2CH_2	61
8	**10**	55	THF	DMEDA	**13**	90

Using these optimized reaction conditions, we screened some commercially available nitrogen substrates and were happy to observe good to excellent yields in all cases (Table 2, entries 6–8). In all of these reactions, only the *E*-isomers were observed.

In conclusion, we found that radical addition of nitrogen radicals to ynol ethers leads to β-functionalized enamides with poor yield. However, we discovered that copper coupling between 1,2-diiodoethene and acyclic or cyclic amides is an excellent procedure for preparing these compounds in high yields with complete stereo-control.

6. Typical procedures for the preparation of *N*-haloamides and *N*-halosulfonamides[5,10]

6.1. *N,N*-Dichlorobenzenesulfonamide (**4a**)

A reaction vial was charged with benzenesulfonamide **3a** (2.36 g, 15 mmol) and methylene chloride (60 mL). The mixture was cooled to 0 °C. Trichloroisocyanuric acid (2.44 g, 10.5 mmol) was added slowly. The reaction mixture was allowed to warm up to room temperature and stirred overnight and then cooled to 0 °C. The mixture was then filtered on Celite. The solution was evaporated under reduced pressure affording 3.18 g (94%) of a white powder (**4a**). The crude product (98% active chlorine, determined by iodometry) was used without further purification.

6.2. *N,N*-Dichlorourethane (**4c**)

A solution of urethane **3c** (1.07 g, 12 mmol) in acetone (9 mL) and methylene chloride (9 mL) was cooled to 0 °C. Trichloroisocyanuric acid (3.6 g, 15.5 mol) was added slowly. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent was removed under reduced pressure. Hexane (100 mL) was added and the mixture was stirred for 15 min. After filtration on Celite, the solution was evaporated under reduced pressure affording 1.37 g (72%) of a light yellow oil (**4c**). The crude product (98% active chlorine, determined by iodometry) was used without further purification.

7. Procedure for the reactions between ethoxyacetylene and *N*-halo derivatives[11]

7.1. *N*-(2-Ethoxy-2-chloroethene) succinimide (**7a**)

An oven dried flask was charged with *N*-chlorosuccinimide (67 mg, 0.50 mmol). The flask was capped with a rubber septum and equipped with a needle to allow the intake of air. Methylene chloride (2.5 mL) and a solution of ethoxyacetylene (40% in hexane 250 μL, 1.05 mmol) were added. Triethylborane (1 M in hexane, 50 μL, 0.050 mmol) was introduced with a syringe and the mixture was stirred for 30 min. Triethylborane solution (50 μL, 0.050 mmol) was added again after 1 h and after 2 h. The mixture was stirred until the starch-iodide paper test was negative. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography affording 35.6 mg (35%) of a brown oil (**7a**). ^{1}H NMR (200 MHz, $CDCl_3$), *J* (Hz): δ 1.26 (t, *J* = 7, 3H), 2.76 (s, 4H), 4.10 (q, *J* = 7, 2H), 5.53 (s, 1H). ^{13}C NMR, δ (50 MHz, $CDCl_3$), δ 14.8, 28.5, 68.0, 98.9, 145.8, 175.1. IR (neat, cm^{-1}): 3482 (m), 3096 (s), 2939 (m), 1740 (w), 1610 (s). Mass spectrum: *m*/*e* (% relative intensity) 203 (15), 168 (40), 139 (100), 111 (54), 84 (45), 55 (49).

7.2. *N*-(2-Ethoxy-2-iodoethene) succinimide (**7b**)

An oven dried flask was charged with *N*-iodosuccinimide (273 mg, 1.21 mmol) and methylene chloride (11 mL). The mixture was cooled in an ice bath before ethoxyacetylene (40% in hexane, 325 μL, 1.36 mmol) was added slowly under nitrogen atmosphere. The mixture was stirred at 5 °C until the starch-iodide paper test was negative. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography affording 61 mg (17%) of a brown oil (**7b**). ^{1}H

NMR (200 MHz, $CDCl_3$), J (Hz): δ 1.29 (t, $J = 7$, 3H), 2.80 (s, 4H), 3.8 (q, $J = 7$, 2H), 5.53 (s, 1H). ^{13}C NMR, (50 MHz, $CDCl_3$): δ 15.1, 28.5, 60.14, 66.9, 143.5, 174.7. IR (neat, cm^{-1}): 3485 (s), 3260(w), 3087 (s), 2939 (m), 1716 (w), 1346 (m). Mass spectrum: *m/e* (% relative intensity) 295 (7), 168 (100), 100 (17), 55 (13).

8. General procedure for the copper-catalyzed coupling between amide derivatives and 1,2-diiodoethene

1,2-Diiodoethene was prepared from acetylene according to the method described by Wright and Lowe-Ma.[9]

A screw cap test tube was charged with CuI (0.4 mmol, 13 mol %), *N*,*N*′-dimethyl ethylenediamine (0.6 mmol, 20 mol %) and THF (1 mL). The mixture was stirred for 15 min. Cesium carbonate (6 mmol) and a solution containing the amide (3 mmol), 1,2-diiodoethene (4.2 mmol) and THF (2.6 mL) were added. The reaction tube was capped in a nitrogen filled bag. The reaction tube was immersed in a preheated oil bath, and the reaction mixture was stirred for 24 h at 55 °C. The reaction mixture was cooled to room temperature, and the resulting suspension was diluted with methylene chloride (10 mL) and filtrated. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography to provide the desired product.

8.1. *N-(2-Iodoethene)-2-pyrrolidinone* (**12a**)

Yellow solid. Mp 85–87 °C. ^1H NMR (200 MHz, $CDCl_3$), J (Hz): δ 2.35 (m, 2H), 2.40 (t, $J = 8$, 2H), 3.46 (d, $J = 7$, 2H), 5.3 (d, $J = 14$, 1H), 7.5 (d, $J = 14$, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.5, 30.8, 44.7, 55.4, 134.7, 172.4. IR (neat, cm^{-1}): 3338 (s), 3062 (s), 2959 (m), 2884 (s), 1690 (w), 1611 (s), 1482 (s), 1454 (s), 1393 (s), 1325 (s). Mass spectrum: *m/e* (% relative intensity): 237 (87), 182 (63), 153 (21), 127 (30), 110 (100), 82 (47), 55 (68), 41 (57). HRMS: *m/z* calcd for C_6H_8INO: 236.965; found 236.965.

8.2. *N-(2-Iodoethene)-2-oxazolidinone* (**12b**)

Yellow solid. Mp dec 71 °C. ^1H NMR (200 Hz, $CDCl_3$), J (Hz): δ 3.69 (t, $J = 8$, 2H), 4.40 (t, $J = 8$, 2H), 5.21 (d, $J = 14$, 1H), 7.23 (d, $J = 14$, 1H). ^{13}C NMR (50 Hz, $CDCl_3$): δ 42.1, 53.1, 62.6, 134.6, 154.4.IR (neat, cm^{-1}): 3077 (s), 1761 (w), 1613 (s), 1474 (s), 1409 (s). Mass spectrum: *m/e* (% relative intensity) 239 (59), 180 (56), 153 (61), 127 (41), 112 (100), 41 (70). HRMS: *m/z* calcd for $C_5H_6INO_2$: 238.944; found 238.944.

8.3. *N-(2-Iodoethene)-2-piperidinone* (**12c**)

Yellow solid. Mp dec 140 °C. ^1H NMR (200 MHz, $CDCl_3$), J (Hz): δ 1.83 (m, 4H), 2.45 (t, $J = 6$, 2H), 3.38 (t, $J = 6$, 2H), 5.4 (d, $J = 14$, 1H), 8.0 (d, $J = 14$, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6, 22.5, 32.9, 45.1, 55.3, 137.7, 167.9. IR (neat, cm^{-1}): 3258 (s), 3073 (s), 2948 (s), 2872 (s), 2357 (s), 1646 (w), 1600 (s), 1475 (s), 1455 (s), 1427 (s), 1401 (s), 1345 (s). Mass spectrum: *m/e* (% relative intensity): 251 (27), 153 (9), 124 (100), 96 (9), 82 (41), 69 (17), 55 (48), 41 (43). HRMS: *m/z* calcd for $C_7H_{10}INO$: 250.981; found 250.981.

8.4. *N-(2-Iodoethene) acetanilide* (**13**)

Yellow solid. Mp.103–104 °C. ^1H NMR (200 MHz, $CDCl_3$), J (Hz): δ 1.8 (s, 3H), 4.75 (d, $J = 14$, 1H), 7.14 (m, 2H), 7.42 (m, 3H), 8.10 (d, $J = 14$, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.0, 58.3, 128.9, 129.5, 130.6, 138.6, 168.0. IR (neat, cm^{-1}): 3326 (s), 3060 (d), 1676 (w), 1608 (s), 1591 (s), 1487 (s), 1451 (s), 1371 (s). Mass spectrum: *m/e* (% relative intensity) 287 (6), 245 (9), 160 (100), 118 (83), 117 (53), 91 (34), 77 (25), 51 (24), 43 (60). HRMS: *m/z* calcd for $C_{10}H_{10}INO$: 286.981; found 286.981.

Acknowledgments

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10. Compounds previously reported in the literature were characterized by comparing their ^1H NMR spectra to the published data.
11. Enamides **7a** and **7b** were not sufficiently stable to allow HRMS characterization.