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Cupric chloride promoted regioselective C-allylation of enaminones

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Abstract

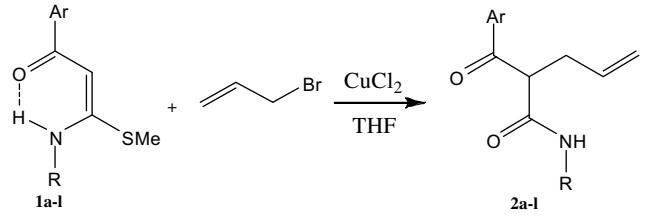
Regioselective allylation of enaminones using $CuCl_2$ as the catalyst to give C-allylated products is reported for the first time. The C-allylated products undergo hydrolysis followed by a rearrangement yielding β-keto allyl enamides in excellent yields.

Keywords: Allylation; Enaminone; β-Keto allyl enamides; Ketene *N*,*S*-acetal

Cuprous and cupric salts are used as effective catalysts in several oxidative ring cyclization reactions,[1] and in the presence of oxygen and pyridine or amino ligands, they are considered as useful oxidizing systems for cleavage of hydrazides.[2] Another interesting application of copper salts is in the addition reaction of allylmetals to C=Z bonds (Z = O or NR), which has emerged as a very useful carbon–carbon bond-forming reaction.[3] Metal-catalyzed allylic substitution is a useful process in organic synthesis for C–C and C–heteroatom bond forming reactions.[4] However, these approaches are still extremely limited in scope and functional group compatibility. Moreover, despite the potential utility of allylated β-keto amides as synthetic intermediates, their synthesis using copper salts as catalyst has been rarely studied.[5]

We reported some years ago the synthesis of biologically important 2,3-functionalized imidazo[1,2-*a*]pyridines via an unprecedented $CuCl_2$-induced oxidative ring closure of certain α-oxoketene *N*,*S*-, *N*,*O*- and *N*,*N*-acetal intermedia-tes.[6] Ketene *N*,*S*-acetals are highly versatile enamines widely used in the synthesis of heterocycles.[7] Junjappa and co-workers have recently reported the synthesis of substituted quinolines and quinoxalines via cyclization of ketene *N*,*S*-acetals under Vilsmeier–Haack conditions.[8] We now report a facile synthesis of β-keto allyl enamides via regioselective allylation of *N*,*S*-acetals using cupric chloride as the catalyst.

Ketene *N*,*S*-acetals were prepared starting from ketene dithioacetals by displacement of the thiomethyl groups by the respective amines either in refluxing ethanol or in tetrahydrofuran.[9] Our various trial experiments to prepare either the C- or the N-allylated products of the ketene *N*,*S*-acetals, by treating **1a–l** with allyl bromide without using any catalyst in various solvents, resulted in failure. Thus refluxing *N*,*S*-acetals **1a–l** and allyl bromide in solvents such as ethanol, acetonitrile and tetrahydrofuran gave no significant results. Surprisingly, we observed the formation of β-keto enamides **2a–l** in excellent yields by treating the *N*,*S*-acetals and allyl bromide directly in the presence of cupric chloride and refluxing in THF for 2–3 h (Scheme 1).[10]



Scheme 1.

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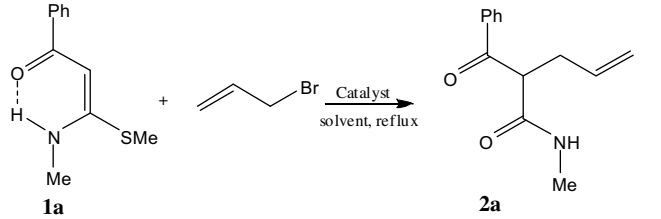
In order to evaluate the scope of this catalytic system, the range of metal salts was extended to various metal halides and acetates as shown in Table 1, guided by the template reaction between ketene *N*,*S*-acetal **1a** and allyl bromide. The $CuCl_2$/THF combination was found to be the best affording the highest yield of 90% after refluxing for 3 h. Screening of different solvents revealed that THF was the most suitable. It was also observed that $ZnCl_2$ and $SnCl_2$ gave good yields of the product, while $MgCl_2$, $AlCl_3$, $FeCl_3$, $BiCl_3$ and $LaCl_3$ gave poor yields of the desired products (Table 1). Moreover, it is noteworthy to mention that no C-allylation occurred in the absence of catalyst (Table 1, entry 15).

After optimizing the reaction conditions, we investigated the generality of this process. As can be seen from Table 2, various ketene *N*,*S*-acetals **1a–l** were C-allylated with allyl bromide to give the corresponding products in good to excellent yields.

We wanted to confirm that the reaction pathway occurred via C-allylation rather than N-allylation. For this study, we required N-allylated ketene *N*,*S*-acetals **3a–l** (Scheme 2) and it was anticipated that N-allylated adducts 3a–**l** might undergo a 3-aza-Claisen rearrangement to give C-allylated products.[11] Recently, Oshima et al. reported[12] a facile method of synthesizing 2,2-disubstituted-4-pentenenitriles via aza-Claisen rearrangement of *N*-allyl-*N*-(phenylethynyl)arenesulfonamides. Thus, as shown in Scheme 2, we treated *N*,*S*-acetals **1a–l** with allyl bromide at 0 °C to 25 °C in the presence of 2 equiv of sodium hydride in tetrahydrofuran and generated *N*,*S*-acetals **3a–l** in very low yields (10–15%).[13]

Table 1
Optimization of the reaction conditions for the C-allylation of **1a** with allyl bromide[a]

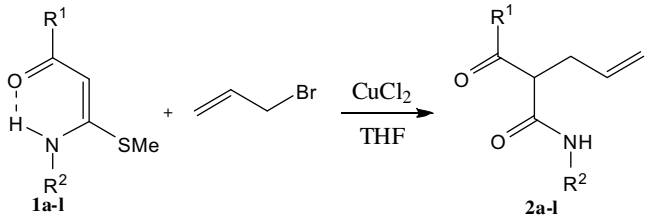


1a **2a**

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$CuCl_2$	DMF	6	65
2	$CuCl_2$	Benzene	10	60
3	$CuCl_2$	Toluene	5	60
4	$CuCl_2$	THF	3	90
5	$CuBr_2$	THF	6	60
6	CuI_2	THF	6	45
7	$Cu(OAc)_2$	THF	5	45
8	$MgCl_2$	Toluene	12	10
9	$AlCl_3$	Toluene	12	20
10	$FeCl_3$	Toluene	10	35
11	$BiCl_3$	Toluene	10	15
12	$LaCl_3$	Toluene	8	10
13	$ZnCl_2$	THF	6	50
14	$SnCl_2$	THF	6	50
15	None	THF	24	0

[a] *N*,*S*-Acetal (5.0 mmol), allyl bromide (5.1 mmol), catalyst (5.0 mmol), solvent (20–30 mL).

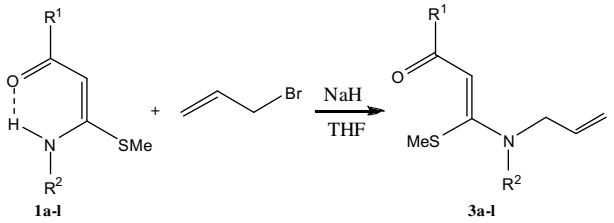
Table 2
β-Keto allyl enamides **2a–l** produced via C-allylation of ketene *N*,*S*-acetals **1a–l**[a]



1a-l **2a-l**

Entry	R^1	R^2	Product	Yield (%)	Mp (°C)
1	C_6H_5	CH_3	**2a**	90	103
2	C_6H_5	C_2H_5	**2b**	92	120
3	C_6H_5	C_3H_7	**2c**	86	105
4	C_6H_5	$CH_2C_6H_5$	**2d**	85	120
5	4-MeC_6H_4	CH_3	**2e**	90	122
6	4-MeC_6H_4	C_2H_5	**2f**	92	113
7	4-MeC_6H_4	C_3H_7	**2g**	90	107
8	4-MeC_6H_4	$CH_2C_6H_5$	**2h**	80	125
9	4-$MeOC_6H_4$	CH_3	**2i**	91	125
10	4-$MeOC_6H_4$	C_2H_5	**2j**	92	94
11	4-$MeOC_6H_4$	C_3H_7	**2k**	92	122
12	4-ClC_6H_4	CH_3	**2l**	90	92

[a] Reaction conditions: *N*,*S*-acetal (5.0 mmol), allyl bromide (5.0 mmol), $CuCl_2$ (5.0 mmol), THF (30 mL), 3 h, reflux.



1a-l **3a-l**

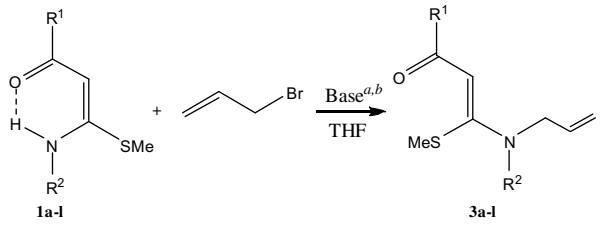
Scheme 2.

During optimization of the reaction conditions, the effect of a number of factors was investigated, including the nature of the base, solvent, the temperature (ranging from 0 °C to reflux), substrate concentration and reaction time. The best yields were obtained using NaH/THF at 25 °C under N_2 and stirring for 10 h giving a 15% yield (Table 3).

Subsequently, *N*,*S*-acetals **3a–l** were submitted to possible intramolecular rearrangements in the presence of cupric chloride and Lewis acids ($AlCl_3$, $ZnCl_2$, EtO–BF_3). However, under these conditions, only inseparable by-products were formed and none of the reactions yielded the β-keto enamides **2a–l** (Scheme 3). Thus the possible mechanism for the formation of the C-allylated products from N-allylated adducts **3a–l** via a 3-aza-Cope rearrangement was ruled out. This implied that C-allylation rather than N-allylation was highly favourable in presence of the metal halide and Lewis acid catalytic conditions.

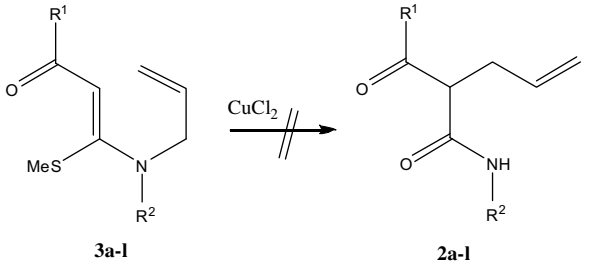
Compounds **2** existed as enamides as evident from their spectral data.[14] Compounds **2** exhibited ethylenic proton

Table 3
Base catalyzed synthesis of *N*,*S*-allylated ketene *N*,*S*-acetals **3a–l**[a,b]



Entry	R^1	R^2	Product	Yield (%)
1	C_6H_5	CH_3	**3a**	15
2	C_6H_5	C_2H_5	**3b**	10
3	C_6H_5	C_3H_7	**3c**	10
4	C_6H_5	$CH_2C_6H_5$	**3d**	5
5	4-MeC_6H_4	CH_3	**3e**	10
6	4-MeC_6H_4	C_2H_5	**3f**	10
7	4-MeC_6H_4	C_3H_7	**3g**	10
8	4-MeC_6H_4	$CH_2C_6H_5$	**3h**	0
9	4-$MeOC_6H_4$	CH_3	**3i**	15
10	4-$MeOC_6H_4$	C_2H_5	**3j**	5
11	4-$MeOC_6H_4$	C_3H_7	**3k**	5
12	4-ClC_6H_4	CH_3	**3l**	15

[a] Reaction condition: *N*,*S*-acetal (5.0 mmol), allyl bromide (5.1 mmol), NaH (5.5 mmol), THF (30 mL), stirring 10 h 0 °C to rt.
[b] The use of Et_3N/THF instead of NaH resulted in no product.



Scheme 3.

signals as multiplets at 4.98–5.10 ppm in the ^{1}H NMR spectra and two carbonyl signals at 167–170 (amide) and 197.5–198.8 (benzoyl) ppm in the ^{13}C NMR spectra. The IR spectra clearly showed the presence of two strong carbonyl peaks. In the case of **2a**, the disappearance of the vinylic proton and the observation of allylic methylene protons at δ 2.60–2.70 ppm as a multiplet in the ^{1}H NMR spectra indicated C-allylation rather than N-allylation.

In conclusion, we have successfully demonstrated the metal catalyzed C-allylation of enaminones yielding β-keto enamides in excellent yields. The best yields were obtained using $CuCl_2$ as the catalyst and refluxing the enaminones with allyl bromide in tetrahydrofuran. Further studies on the mechanism and the role of $CuCl_2$ are being investigated in our laboratory.

Acknowledgments

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Supplementary data

Detailed synthetic and isolation procedures and full spectral identifications of the reported compounds **2a–l** and **3a** are provided. All known *N*,*S*-acetals **1a–l** were prepared by earlier reported procedures.[7a,9] Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.093.

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10. *General procedure for the preparation of* **2a–l**: An equimolar mixture of *N*,*S*-acetal **1**, allyl bromide (5 mmol) and $CuCl_2$ (0.67 g, 5 mmol) in THF (30 mL) was refluxed for 3 h with stirring (monitored by TLC). Then, the mixture was brought to room temperature and $CuCl_2$ was filtered through a sintered funnel. The filtrate was concentrated under reduced pressure and poured into water and extracted with chloroform (3 × 50 mL). The combined organics were washed with H_2O (2 × 50 mL) and dried over Na_2SO_4. The solvent was evaporated under vacuum to give compounds **2**, which were purified by column chromatography over silica gel using hexane/EtOAc (10:1) as eluent. Compound **2a**: Mp 103 °C; IR (KBr): 1556, 1633, 1681, 2917, 3303 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60–2.75 (m, 2H), 2.75 (d, J = 5 Hz, 3H), 4.44 (t, J = 9 Hz, 1H), 4.98–5.10 (m, 2H), 5.60–5.80 (m, 1H), 6.50 (br s, 1H), 7.45–7.50 (m, 2H), 7.57–7.62 (m, 1H), 7.99–8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 26.5, 28.0, 54.1, 115.5, 128.1, 128.8, 132.2, 137.9, 168.9, 197.8; *m*/*z*: (M^+, %): 217 (M^+, 10),

216 (20), 202, 189, 105 (100); Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.78; H, 6.90; N, 6.51.
Compound **2e**: Mp 122 °C; IR (KBr): 1184, 1546, 1639, 1678, 3288 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.63–2.71 (m, 2H), 2.75 (d, $J = 5$ Hz, 3H), 4.41 (t, $J = 9$ Hz, 1H), 4.97–5.07 (m, 2H), 5.66–5.76 (m, 1H), 6.50 (br s, 1H), 7.24 (d, $J = 9$ Hz, 2H), 7.88 (d, $J = 9$ Hz, 2H); 13C ($CDCl_3$, 100 MHz): 21.5, 26.5, 33.9, 55.3, 117.5, 128.1, 129.5, 134.0, 134.9, 145.0, 168.3, 198.8; *m/z*: (M^+, %): 231 (M^+, 8), 216 (10), 140, 119 (100); Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.48; N, 6.01.

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13. *General procedure for the preparation of* **3a–l**: NaH (5.5 mmol) was added slowly to a solution of the ketene *N*,*S*-acetal **1a–l** (5 mmol) in dry THF (30 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 20 min, then allyl bromide (5.2 mmol) was added and stirring was continued for 2 h at the same temperature. The reaction mixture was brought to room temperature and stirring was continued for 10 h (monitored by TLC). The reaction mixture was poured into crushed ice and extracted with chloroform (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 50 mL), dried over Na_2SO_4, concentrated and purified by column chromatography over silica gel using hexane/EtOAc as eluent to yield **3a–l**
Compound **3a**: Viscous oil; IR (KBr): 1250, 1655, 2910, 3309 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.50 (s, 3H), 2.81 (d, $J = 5$ Hz, 2H), 2.96 (s, 3H), 4.98–5.25 (m, 2H), 5.80 (s, 1H), 5.85–5.95 (m, 1H), 7.45–7.50 (m, 2H), 7.56–7.62 (m, 1H), 7.86–7.97 (m, 2H); ^{13}C ($CDCl_3$, 100 MHz): 20.1, 38.0, 54.1, 95.5, 118.2, 128.1, 128.8, 132.2, 137.9, 165.1, 187.8; *m/z*: (M^+, %): 247 (M^+,5), 216 (20), 105 (100); Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.92; H, 6.90; N, 5.31.
14. All the products were characterized from spectral and analytical data.