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Synthesis of aryl α-keto-acids via the Cu-catalyzed conversion of aryl nitroaldol products

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Abstract

Cu(II) salts efficiently catalyze the conversion of a variety of aryl nitroaldol products to afford the corresponding aryl α-keto-acids in high yields using 30% aq. AcOH:MeOH (1:1) as the solvent.

Keywords: nitroaldol; conversion; catalyst; keto-acid.

We wish to report a new catalytic method for the synthesis of α-keto-acids in a single step from a variety of aryl nitroaldol products, prepared from Henry reactions.[1] Several synthetic procedures have been reviewed in the literature for the synthesis of α-keto-acids which involve multiple steps or use costly or hazardous reagents.[2] The use of stoichiometric anhydrous $CuSO_4$ has been reported for the conversion of 1-alkyl-2-nitrocyclohexanols to nitroketones via a retro-Henry reaction.[3] We here report that catalytic Cu-salts in 30% aq. AcOH:MeOH (1:1) can be useful for the conversion of aryl nitroaldol products into aryl α-keto-acids (Scheme 1). Table 1 shows a comparative study of the use of Cu-salts and other oxidizing reagents for the conversion of aryl nitroaldol products to α-keto-acids.

The results of Cu(II)-salt catalyzed conversion of aryl nitroaldol products to the corresponding α-keto-acids† is summarized in Table 2. The catalytic activity of $CuSO_4 \cdot 5H_2O$ was found to be low when compared to $Cu(OAc)_2 \cdot H_2O$ towards the reaction. It was observed that, for aryl nitroaldol products

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† Typical experimental procedure: A mixture of 1-(4-chlorophenyl)-2-nitroethanol (0.5 g; 2.48 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.05 g, 10 mol%) and 30% aq. AcOH:MeOH (1:1, 10 ml) was heated under reflux at 90°C (bath temperature) for 3 h. After 1 h, progress of the reaction could be seen by the formation of a solid product precipitating from the reaction mixture (also monitored by TLC, 15% EtOAc in pet-ether). The reaction mixture was then poured into water and extracted with EtOAc (25 ml×3) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude α-keto-acid (0.45 g) which was purified by column chromatography (7% EtOAc in pet-ether). Yield: 93%; m.p. 92–94°C; IR (cm^{-1}): 3045, 2924, 1775, 1702, 1674, 1576, 1592, 1490, 1206, 1102, 968, 942; ^{1}H NMR (200 MHz, $CDCl_3$): δ (7.37, d J=8 Hz, 2H), (7.85, d J=8 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 129.62, 130.59, 135.19, 141.05, 165.02, 191.13; MS: *m/z* (% rel. intensity): M^+, 184(1), 183(10), 166(1), 148(20), 136(67), 125(15), 101(100), 89(21), 75(50) 63(3), 57(1). Anal. $C_8H_5ClO_3$: requires: C, 52.06, H, 2.73, Cl, 19.21%; found: C, 51.99, H, 2.70, Cl, 19.01%.

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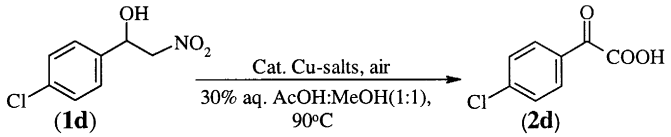
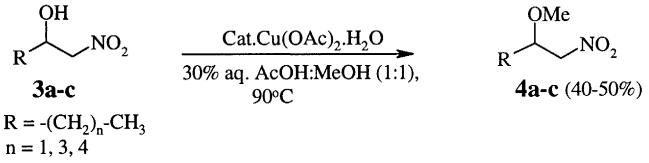
Table 1
Reactions of 1-(4-chlorophenyl)-2-nitroethanol (**1d**) with various catalysts[a]

No	Reagent/Catalyst	Reaction condition	T/h	Product (**2d**)	Yield (%)[b]
1	MnO_2	Benzene, 80 °C	8	2-(4-Chlorophenyl)-2-oxoacetic acid	46
2	DMSO-oxalyl chloride-Et_3N	CH_2Cl_2, -43 °C	4	2-(4-Chlorophenyl)-2-oxoacetic acid	60
3	$Cu(OAc)_2.H_2O$	30% aq. AcOH:MeOH (1:1), 90 °C	4	2-(4-Chlorophenyl)-2-oxoacetic acid	93
4	$CuSO_4.5H_2O$	30% aq. AcOH:MeOH (1:1), 90 °C	4	2-(4-Chlorophenyl)-2-oxoacetic acid	97
5	$CuCl_2$	30% aq. AcOH:MeOH (1:1), 90 °C	4	2-(4-Chlorophenyl)-2-oxoacetic acid	90
6	CuI	30% aq. AcOH:MeOH (1:1), 90 °C	4	2-(4-Chlorophenyl)-2-oxoacetic acid	70

a: Nitroaldol product (5 mmol); catalyst (10 mol%); solvent (10 ml); b: Isolated yield after chromatographic purification;



Scheme 1.



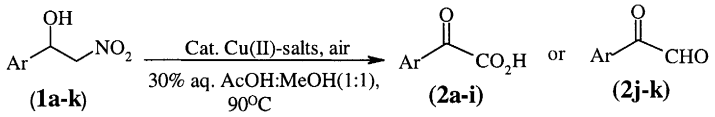
Scheme 2.

bearing electron-withdrawing groups such as NO_2 and CN, the rate of reaction is slower than for substrates with electron-donating groups. It is remarkable that in the case of substrates with NO_2 and quinoline moieties (entries 1j–k), the reaction stops at the keto-aldehyde stage without undergoing further oxidation to the corresponding acid. Under similar conditions aliphatic analogues (**3a–c**) undergo reaction to produce nitroalkyl ethers (**4a–c**) instead of undergoing conversion to α-keto-acids (Scheme 2).

Analysis of the reaction mixture hourly using ^1H NMR spectroscopy indicated that the reaction mixture contained both the α-keto-aldehyde and the α-keto-acid. As time progressed, the yield of α-keto-acid increased with a concurrent decrease of α-keto-aldehyde.

In conclusion, the results described herein demonstrate the novelty of Cu-salts as efficient catalysts for the conversion of aryl nitroaldol products to the corresponding α-keto-acids in high yields. For aliphatic analogues, nucleophilic displacement with MeOH leads to the formation of nitroalkyl ethers in moderate yields instead of the conversion to α-keto-acids. It may be noted that α-keto-acids are of biological interest as intermediates in amino acid metabolism, as participants in the citric acid cycle and as intermediates in other biological reactions.[4]

Table 2
Cu(II)-catalyzed conversion of aryl nitroaldol products to α-keto-acids[a]



No	Substrate Ar (1)	t/h	Product[b] (2)	Yield[c] (%) Cu[d]	Yield[c] (%) Cu[e]	m.p.°C[f]
1a	Ph	4	2-Oxo-2-phenylacetic acid	61	45	67-69 (66)
1b	4-Methylphenyl	4	4-Methylphenyl-2-oxoacetic acid	88	50	97-99 (97)
1c	4-Methoxyphenyl	4	2-(4-Methoxyphenyl)-2-oxoacetic acid	87	–	93-95 (93)
1d	4-Chlorophenyl	3	2-(4-Chlorophenyl)-2-oxoacetic acid	93	97	92-94 (92-93)
1e	4-Cyanophenyl	5	2-(4-Cyanophenyl)-2-oxoacetic acid	41	35	138 (dec.)
1f	3,4,5–Trimethoxyphenyl	3	2-(3,4,5-Trimethoxyphenyl) -2-oxoacetic acid	80	41	114-115
1g	3-Nitro-4-methylphenyl	4	2-(3-Nitro-4-methylphenyl)-2-oxoacetic acid	75	60	165-167
1h	2-Naphthyl	4	2-Oxo-2-naphthylacetic acid	59	–	90-92 (91-92)
1i	2-Furyl	4	2-Oxo-2-furylacetic acid	72	–	98-100 (98)
1j	4-Nitrophenyl	5	2-(4-Nitrophenyl)-2-oxo-acetaldehyde	50	30	95-97
1k	3-Chloro-2- quinolinyl	4	2-(3-Chloroquinolinyl)-2-oxoacetaldehyde	41	–	112-115

a) Nitroaldol product (5 mmol); Cu(II) catalyst (10 mol%), 30% aq.AcOH : MeOH (1:1, 15 ml), 90 °C; b) Thoroughly characterized by IR, ^{1}H & ^{13}C NMR, MS and elemental analysis; c) Isolated yield after chromatographic purification; d) $Cu(OAc)_2.H_2O$; e) $CuSO_4.5H_2O$; f) Number in parenthesis refers to literature m.p.

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