Tetrahedron Letters 55 (2014) 1323–1325

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper-catalyzed S-arylation of tetramethylguanidine–heterocumulene adducts

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ARTICLE INFO

Article history:
Received 6 October 2013
Revised 28 November 2013
Accepted 2 January 2014
Available online 9 January 2014

Keywords:
Ullmann coupling
Carbamodithioates
Copper-catalyzed
Heterocumulenes
S-arylation

ABSTRACT

The synthesis of a novel class of aryl bis(dimethylamino)methylenecarbamodithioates via a copper-catalyzed S-arylation reaction of 1,1,3,3-tetramethylguanidine–heterocumulene adducts is described.

Cross-coupling reactions using transition metal catalysis represent a powerful tool for the formation of carbon–heteroatom bonds.[1–6] Copper-catalyzed coupling reactions were first reported by Ullmann,[7] and have found increasing utility for the construction of carbon-heteroatom bonds.[8–10] Although several copper-catalyzed reactions have been reported for $C_{(aryl)}$–N and $C_{(aryl)}$–O, $C_{(aryl)}$–S bond formation is much less investigated. Carbon–sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds.[11–13] Sulfur is present in many molecules that are of biological, pharmaceutical, and material interest.[14] Thus, the investigation of new protocols for C–S bond generation, which can lead to the discovery of less expensive and more efficient synthetic methods for the preparation of organo-sulfur compounds has attracted much attention in recent years.[15–17]

Organic dithiocarbamates are important in medicinal[18] and agricultural chemistry.[19] These compounds are used in the rubber industry as vulcanization accelerators,[20] in controlled radical polymerization techniques,[21] and in the synthesis of ionic liquids.[22] *S*-Aryl-isothioureas[23,24] are starting materials for the synthesis of guanidines and heterocyclic systems.[25,26] It has been recognized that they can also serve as remarkably potent inhibitors for a whole range of enzyme systems.[27–29] Inhibition of nitric oxide synthase has led to their use in the treatment of a range of life-threatening conditions including septic shock, acute kidney failure, and organ rejection after transplantation surgery.[30]

Mild and efficient methods for the synthesis of carbamimidothioates and dithiocarbamates have attracted widespread interest due to their diverse biological activities. Consequently, several methods have been developed for the construction of these compounds.[31–33] The biological and synthetic significance places this scaffold in a privileged position in medicinal chemistry research. Thus we have investigated copper-catalyzed $C_{(aryl)}$–S bond formation using isothiocyanates or carbon disulfide, 1,1,3,3-tetramethylguanidine, and aryl halides.[34]

Initially, iodobenzene (**1a**), phenylisothiocyanate (**2a**) or carbon disulfide (**2m**), and 1,1,3,3-tetramethylguanidine (**3**) were selected as the model substrates. Several catalysts including CuI, CuBr, CuCl, Cu_2O, and copper powder were tested with CuI giving the best

Table 1
Optimization of the reaction conditions for the formation of compound **5a** from iodobenzene (**1a**), phenylisothiocyanate or CS_2, and tetramethylguanidine (**3**)

Catalyst[a]	Solvent	Yield[b] (%)	Catalyst[a]	Solvent	Yield[b] (%)
Cu_2O	DMF	43	CuI	Toluene	46
Cu_2O	MeCN	32	CuI	DMSO	41
Cu_2O	Toluene	17	CuI	THF	26
CuCl	DMF	61	CuBr	DMF	62
CuCl	MeCN	54	CuBr	Toluene	31
CuCl	Toluene	33	CuBr	DMSO	24
CuI[c]	DMF	83	Cu	DMF	—
CuI	MeCN	70	Cu	Toluene	—

[a] 10 mol % of catalyst was used unless otherwise stated.
[b] Reaction time = 10 h.
[c] 5 mol % of catalyst was used; reaction time = 25 h.

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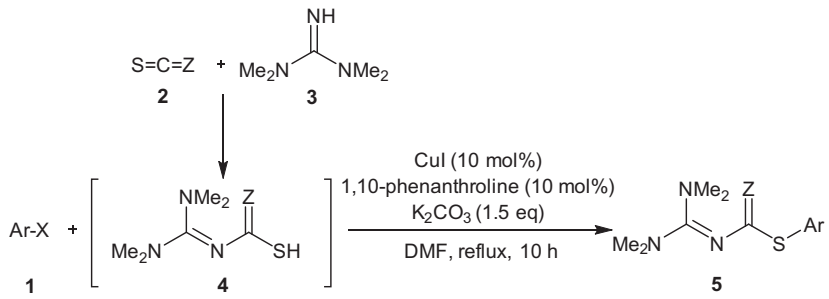
0040-4039/$ - see front matter © 2014 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetlet.2014.01.006



1,2,4,5	X	Z	Ar	Yield (%) of **5**
a	I	N-Ph	Ph	83
b	I	N-Ph	4-Me-C_6H_4	87
c	I	N-Ph	4-Br-C_6H_4	79
d	I	N-Ph	4-Cl-C_6H_4	77
e	I	N-Ph	4-MeO-C_6H_4	73
f	I	N-C_6H_4-4Cl	Ph	76
g	I	N-C_6H_4-4Cl	4-Me-C_6H_4	72
h	I	N-C_6H_4-4NO_2	Ph	79
i	I	N-C_6H_4-4NO_2	4-Me-C_6H_4	74
j	Br	N-Ph	3-Me-C_6H_4	65
k	Br	N-Ph	3-O_2N-C_6H_4	69
l	Br	N-Ph	2-thienyl	60
m	I	S	Ph	82
n	I	S	4-Me-C_6H_4	83
o	I	S	4-Br-C_6H_4	78
p	I	S	4-Cl-C_6H_4	75
q	Br	S	2-thienyl	70
r	Br	S	3-NO_2-C_6H_4	71

Scheme 1. Copper-catalyzed C–S coupling of aryl halides with 1,1,3,3-tetramethylguanidine and heterocumulenes.

results. Among several solvents screened, *N,N*-dimethylformamide (DMF) was the best. Thus, the optimized reaction conditions used were: 10 mol % of CuI as the catalyst, 10 mol % of 1,10-phenanthroline as the ligand, 1.5 mmol of K_2CO_3 as the base, 1 mmol of 1,1,3,3-tetramethylguanidine, and 1 mmol of isothiocyanate or 1.5 mmol of carbon disulfide in DMF (see Table 1).

Using the optimized conditions, various carbamimidothioates were prepared from isothiocyanates, 1,1,3,3-tetramethylguanidine, aryl iodides and aryl bromides. Aryl bromides served as low yielding substrates compared to aryl iodides (see Scheme 1).

The structures of products **5a**–**r** were assigned from IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **5a** exhibited two singlets for the dimethylamino (2.74, 2.86 ppm) protons, along with characteristic multiplets for the phenyl protons. The ^{13}C NMR spectrum of **5a** exhibited 12 signals in agreement with the proposed structure. The mass spectrum of **5a** displayed the molecular ion peak at $m/z = 326$. The NMR spectra of compounds **5b**–**r** were similar to those of **5a**, except for the substituents, which showed characteristic signals in the appropriate regions of the spectra.

Cyanoguanidine reacted with CS_2, but attempts to bring about the subsequent S-arylation failed. Attempts to use guanidinium salts with CS_2 and an aryl iodide led only to complex mixtures from which none of the desired S-arylated product could be obtained.

In conclusion, we have developed an efficient and experimentally simple, copper-catalyzed method for carbon–sulfur bond formation yielding carbamimidothioate derivatives starting from aryl halides, heterocumulenes, and tetramethylguanidine. The potential diversity of this reaction and readily available starting materials and catalysts are the main advantages of this methodology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.006.

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34. *General procedure for the synthesis of compounds* ***5a–r****:* A mixture of **2** (1–1.5 mmol) and **3** (1 mmol) was stirred in DMF (2 mL) for 30 min. Next, a mixture of aryl halide (1 mmol), CuI (0.1 mmol), 1,10-phenanthroline (0.1 mmol), and K_2CO_3 (1.5 mmol) in DMF (3 mL) was slowly added and the resulting mixture stirred at 110 °C, under an N_2 atmosphere. After completion of the reaction [about 10 h; TLC (EtOAc/hexane, 1:5) monitoring], the mixture was diluted with CH_2Cl_2 (2 mL) and aqueous NH_4Cl solution (3 mL), stirred for 30 min, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×3 mL) and the combined organic fractions dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography [silica gel (230–400 mesh; Merck), hexane/EtOAc, 5:1] to give the product.
Phenyl *N*-bis(dimethylamino)methylene-*N*′-phenylcarbamimidothioate (**5a**): Cream powder, mp: 139–141 °C; yield: 0.27 g (83%). IR (KBr) (ν_{max}, cm^{-1}): 2050, 1678, 1580, 1405, 1371, 1172, 1075. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 2.74 (6H, s, NMe_2), 2.86 (6H, s, NMe_2), 7.12 (2H, d, ^3J = 7.4 Hz, Ar), 7.18 (1H, t, ^3J = 7.4 Hz, Ar), 7.24 (2H, t, ^3J = 7.4 Hz, Ar), 7.35 (2H, d, ^3J = 7.5 Hz, Ar), 7.39 (1H, t, ^3J = 7.5 Hz, Ar), 7.65 (2H, t, ^3J = 7.5 Hz, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 41.8 (NMe_2), 44.4 (NMe_2), 125.9 (C), 126.1 (2 CH), 127.7 (C), 128.7 (2CH), 130.0 (CH), 131.5 (CH), 133.7 (2CH), 135.4 (2CH), 166.9 (C), 172.0 (C). EI-MS: *m*/*z* (%) = 326 (M^+, 5), 282 (6), 217 (12), 212 (16), 114 (100), 109 (21), 77 (51), 44 (31). Anal. Calcd for $C_{18}H_{22}N_4S$ (326.16): C, 66.22; H, 6.79; N, 17.16. Found: C, 66.46; H, 6.75; N, 17.21.