ChemComm
www.rsc.org/chemcomm

CuI-catalyzed coupling reaction of aryl halides with terminal alkynes in the absence of palladium and phosphine†

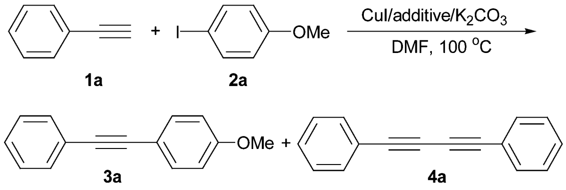
Dawei Ma* and Feng Liu
Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. E-mail: madw@mail.sioc.ac.cn; Fax: 86-21-64166128; Tel: 86-21-64163300

Received (in Cambridge, UK) 13th May 2004, Accepted 7th June 2004
First published as an Advance Article on the web 28th July 2004

CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of aryl halides with terminal alkynes is carried out in DMF at 100 °C to provide the corresponding coupling products in good to excellent yields with a great diversity.

Since its discovery in 1975, Sonogashira coupling has been applied widely in the synthesis of both biologically and synthetically important aryl acetylenes.[1,2] This reaction normally utilizes 1–10 mol% $Pd(PPh_3)_2Cl_2$ (or $Pd(PPh_3)_4$) and copper(I) iodide as the catalytic system, which is problematic for industrial use owing to the cost of palladium. In order to overcome this drawback a great number of efforts have been directed to explore new catalytic systems recently.[3–5] Successful examples include replacement of triphenylphosphine with some special phosphines to enhance the catalytic efficiency[3] and employing less expensive nickel instead of palladium.[4] However, the former suffers from the requirement of less conveniently available phosphines, while the latter still needs two metals, which makes catalyst recovery more difficult. On the other hand, although it has been known for decades that aryl halides could couple with copper(I) acetylides to give aryl acetylenes,[6] there have been few reports concerning the use of copper(I) alone as the catalyst for coupling of aryl halides and terminal alkynes.[7] Of the two known catalytic systems, only aryl iodides worked well and very low yields or no coupling were observed when aryl bromides were used.

In recent years, we have witnessed great progress on the development of mild conditions for traditional Ullmann-type coupling reactions, which highly relied on utilization of some ligands as the promoters.[8,9] In the previous reports, we have demonstrated that the several combinations of CuI/amino acids were efficient catalytic systems for formation of aryl-heteroatom bonds.[10] Herein we wish to disclose a CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of aryl halides with terminal alkynes, which worked at 100 °C to give the coupling products in good to excellent yields.



(1)

Initially, we employed CuI-catalyzed coupling reaction of phenylacetylene with 4-iodoanisole in DMF at 100 °C as a model for discovery of optimised conditions (eqn. (1)). As summarized in Table 1, it was found that without additive this reaction gave trace of desired cross-coupling product **3a**, while homocoupling reaction product **4a** of phenylacetylene was isolated in 55% yield (entry 1). After adding 30 mol% L-proline or *N*-methylglycine, the yields of **3a** were enhanced to moderate and the formation of **4a** was inhibited partially (entries 2 and 3). These results clearly indicated that some amino acids could promote the cross-coupling reaction. Considered that at this reaction temperature both L-proline and *N*-methylglycine might couple with **2a** thereby decreasing the activity of the catalytic system, we decided to use *N*,*N*-dimethylglycine, which is unable to couple with aryl halides, as the additive. As we expected, when 30 mol% *N*,*N*-dimethylglycine hydrochloride salt was used the reaction provided cross-coupling product in 88% yield although a small amount of **4a** was still formed (entry 4). The ratio of 3 : 1 for *N*,*N*-dimethylglycine hydrochloride salt and CuI was necessary to ensure a good result because it was noticed that the lower the ratio used, the more side product formed (compare entries 4–6). In addition, reducing catalyst loading also increased the formation of **4a** (entry 7).

The optimised condition was further tested by varying aryl halides and terminal alkynes. As summarized in Table 2, it was found that either electron-deficient or electron-rich aryl iodides reacted with phenylacetylene to give the corresponding cross-coupling products in 82–98% yields (entries 1–4). More importantly, we were pleased to observe that aryl bromides also worked well for this reaction although higher catalyst loading (20 mol% CuI and 60 mol% additive) was required for obtaining satisfactory yields (entries 5–9). Noteworthy was that a variety of functional groups of aryl iodides and aryl bromides tolerate to this reaction condition, which include alkanoxyl, chloro, fluoro, nitro, carboxylate, ketone and pyridine groups. When 4-chlorophenyl bromide was used, only the product reacted with the C–Br bond was isolated in 94% yield (entry 6), which implied that there existed great selectivity between aryl bromides and aryl chlorides for the present reaction condition. In cases of 4′-chlorophenylacetylene as a coupling substrate, relatively low yields were observed in comparison with that of phenylacetylene (compare entries 3 and 10, 8 and 12), which might result from the lower reactivity of 4′-chlorophenylacetylene-derived anion caused by its electron-withdrawing group. Aliphatic alkynes were also suitable substrates for this reaction besides aryl alkynes. For examples, 1-heptyne and *O*-protected propargyl alcohol coupled with aryl iodides or bromides to provide aryl- and alkyl-substituted acetylenes (entries 13–22). It is notable that *tert*-butyldimethylsilyl ether survived at this reaction condition, which would allow preparing more diverse aryl alkynes (entries 21 and 22). Furthermore, since the present catalyst loading was relatively high, we attempted to run this reaction by increasing the reaction temperature and reducing the amounts of CuI and *N*,*N*-dimethylglycine. It was found that at 120 °C either aryl iodides or aryl bromides still worked to give the cross-coupling products when

Table 1 CuI-catalyzed coupling reaction of 4-iodoanisole with phenylacetylene assisted by additives[a]

		Yield (%)[b]		
Entry	Additive	3a	4a	2a
1	No	< 2	55	48
2	30 mol% L-proline	37	20	34
3	30 mol% $MeNHCH_2CO_2H$	48	9	42
4	30 mol% $Me_2NCH_2CO_2H{\cdot}HCl$	88	5	0
5	20 mol% $Me_2NCH_2CO_2H{\cdot}HCl$	52	28	18
6	10 mol% $Me_2NCH_2CO_2H{\cdot}HCl$	37	40	25
7[c]	12 mol% $Me_2NCH_2CO_2H{\cdot}HCl$	65	22	7

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1 mmol), CuI (0.1 mmol), K_2CO_3 (3 mmol) in 2 mL of DMF, 100 °C, 24 h. [b] Isolated yield. [c] 4 mol% CuI was used and reaction was carried at 110 °C.

---

† Electronic supplementary information (ESI) available: Experimental procedures. See http://www.rsc.org/suppdata/cc/b4/b407090a/

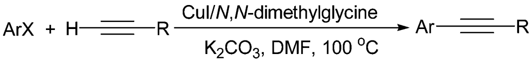
DOI: 10.1039/b407090a

the amounts of both CuI and *N*,*N*-dimethylglycine hydrochloride salt were cut to half, but the yield was slightly lower than that observed before for the corresponding substrates (entries 23–26).

In conclusion, a palladium- and phosphine-free reaction condition for Sonogashira-type coupling was developed, which used CuI/*N*,*N*-dimethylglycine as the catalyst system and was applicable to a range of aryl iodide, aryl bromide, aryl alkyne and aliphatic alkyne substrates. Since this catalyst system is cheap and easily removable (by simple washing), it should find practical usage in synthesis of aryl acetylenes.

Financial support from the Chinese Academy of Sciences, National Natural Science Foundation of China (grants 20321202 & 20132030), and Science and Technology Commission of Shanghai Municipality (grants 02JC14032 & 03XD14001) is acknowledged.

Table 2 CuI/*N*,*N*-dimethylglycine catalyzed coupling reaction of aryl halides with terminal acetylenes[a]



Entry	ArX	R	Time (h)	Yield[b] (%)
1	2-$MeOC_6H_4I$	Ph	36	82
2	4-$HO_2CC_6H_4I$	Ph	24	92[c]
3	3-$O_2NC_6H_4I$	Ph	24	98
4	2-FC_6H_4I	Ph	24	92
5	4-$MeOC_6H_4Br$	Ph	30	92
6	4-ClC_6H_4Br	Ph	24	94
7	3-$HO_2CC_6H_4Br$	Ph	24	96[c]
8	4-$CH_3COC_6H_4Br$	Ph	24	78
9	3-bromopyridine	Ph	24	70
10	3-$O_2NC_6H_4I$	4-ClC_6H_4	24	62
11	4-$MeOC_6H_4I$	4-ClC_6H_4	24	79
12	4-$CH_3COC_6H_4Br$	4-ClC_6H_4	24	60
13	4-$MeOC_6H_4I$	*n*-C_5H_{11}	30	91
14	4-$CH_3COC_6H_4Br$	*n*-C_5H_{11}	30	71
15	4-MeC_6H_4Br	*n*-C_5H_{11}	24	64
16	4-$MeOC_6H_4I$	$BnOCH_2$	24	92
17	2-FC_6H_4I	$BnOCH_2$	24	75
18	4-$HO_2CC_6H_4I$	$BnOCH_2$	24	77[c]
19	4-$MeOC_6H_4Br$	$BnOCH_2$	24	85
20	4-$CH_3COC_6H_4Br$	$BnOCH_2$	24	90
21	4-$MeOC_6H_4I$	$TBDMSOCH_2$	24	88
22	4-MeC_6H_4Br	$TBDMSOCH_2$	24	79
23	4-$MeOC_6H_4I$	Ph	24	85[d]
24	3-$O_2NC_6H_4I$	Ph	24	93[d]
25	4-$MeOC_6H_4Br$	Ph	24	78[d]
26	4-ClC_6H_4Br	Ph	24	73[d]

[a] Reaction conditions: Aryl iodide (1 mmol), acetylene (1.2 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.3 mmol), K_2CO_3 (3 mmol) in 2 mL of DMF, 100 °C; or aryl bromide (1 mmol), acetylene (1.2 mmol), CuI (0.2 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.6 mmol), K_2CO_3 (3 mmol) in 2 mL of DMF, 100 °C. [b] Isolated yield. [c] 4 mmol of K_2CO_3 was used. [d] Reaction was carried out at 120 °C and the amounts of both CuI and *N*,*N*-dimethylglycine hydrochloride salt were reduced to half those used previously.

Notes and references

1 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1999, **vol. 3**, p. 521.

2 For recent examples, see: J. S. Wu, M. D. Watson, L. Zhang, Z. H. Wang and K. Mullen, *J. Am. Chem. Soc.*, 2004, **126**, 177; G. Hennrich and A. M. Echavarren, *Tetrahedron Lett.*, 2004, **45**, 1147; J. N. Wilson, M. Josowicz, Y. Q. Wang and U. H. F. Bunz, *Chem. Commun.*, 2003, 2962; C. C. Li, Z. X. Xie, Y. D. Zhang, J. H. Chen and Z. Yang, *J. Org. Chem.*, 2003, **68**, 8500; K. Y. Tsang, M. A. Brimble and J. B. Bremner, *Org. Lett.*, 2003, **5**, 4425; I. Paterson, R. D. M. Davies, A. L. Heimann, R. Maquez and A. Meyer, *Org. Lett.*, 2003, **5**, 4477; J. W. Lane and R. L. Halcomb, *Org. Lett.*, 2003, **5**, 4017; T. M. Hansen, M. M. Engler and C. J. Forsyth, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2127; N. Ohyaba, T. Nishkawa and M. Isobe, *J. Am. Chem. Soc.*, 2003, **125**, 8798; J. A. Marshall and G. M. Schaaf, *J. Org. Chem.*, 2003, **68**, 7428; S. Lopez, F. Fernandeztrillo, L. Castedo and C. Saa, *Org. Lett.*, 2003, **5**, 3275.

3 For recent references, see: M. Feuerstein, H. Doucet and M. Santelli, *Tetrahedron Lett.*, 2004, **45**, 1603; K. Heuzé, D. Méry, D. Gauss and D. Astruc, *Chem. Commun.*, 2003, 2274; D. Méry, K. Heuzé and D. Astruc, *Chem. Commun.*, 2003, 1934; A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer and D. L. Hughes, *Org. Lett.*, 2003, **5**, 4191; E. Mas-Marzá, A. M. Segqrrq, C. Claver, E. Peris and E. Fernandez, *Tetrahedron Lett.*, 2003, **44**, 6595; N. E. Leadbeater and B. J. Tominack, *Tetrahedron Lett.*, 2003, **44**, 8653.

4 L. Wang, P. Li and Y. Zhang, *Chem. Commun.*, 2004, 514; I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov and N. V. Lukashev, *Tetrahedron Lett.*, 2003, **44**, 5011.

5 For Sonogashira-type couplings using microwave heating, see: H. He and Y. Wu, *Tetrahedron Lett.*, 2004, **45**, 3237; N. E. Leadbeater, M. Macro and B. J. Tominack, *Org. Lett.*, 2003, **5**, 3919.

6 R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 2162; R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313; C. E. Castro, E. J. Gaughan and D. C. Owsley, *J. Org. Chem.*, 1966, **31**, 4071.

7 K. Okuro, M. Furuune, M. Enna, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 4716; R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315.

8 For reviews, see: S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428.

9 For some leading references, see: H.-J. Cristau, P. P. Cellier, S. Hamada and J.-F. Spindler and M. Taillefer, *Org. Lett.*, 2004, **6**, 913; C. Han, R. Shen, S. Su and J. A. Porco, Jr., *Org. Lett.*, 2004, **6**, 27; L. Jiang, G. E. Job, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 3667; G. Nordmann and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 4978; D. van Allen and D. Venkataraman, *J. Org. Chem.*, 2003, **68**, 4590; E. Buck, Z. J. Song, D. Tschaen, P. G. Dormer, R. P. Volante and P. J. Reider, *Org. Lett.*, 2002, **4**, 1623; F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581.

10 D. Ma, Q. Cai and H. Zhang, *Org. Lett.*, 2003, **5**, 2453; D. Ma and Q. Cai, *Org. Lett.*, 2003, **5**, 3799; D. Ma and Q. Cai, *Synlett*, 2004, 128; W. Zhu and D. Ma, *Chem. Commun.*, 2004, 888; X. Pan, Q. Cai and D. Ma, *Org. Lett.*, 2004, **6**, 1809.