Rapid Synthesis of Aryl Azides from Aryl Halides under Mild Conditions

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Abstract: A rapid synthesis of aryl azides from the corresponding aryl halides catalyzed by CuI/diamine is described. Sodium ascorbate was found to have a positive effect on stabilization of the catalyst system. The reactions were performed under very mild conditions generally with high yields. In the case of aryl iodides, the transformation could be carried out at room temperature.

Key words: copper, aryl azides, aryl halides, ligands, azidonation

Aryl azides are used increasingly in organic synthesis, because of versatile transformations of the azide functional group.[1] For example, they can be used for generating anilines and nitrenes,[1] and for the preparation of a variety of hetereocycles.[2] Moreover, aryl azides have found wide utility as photoaffinity probes/labels due to their ability to be made radioactive with high specific activities.[3]

In one of our ongoing medicinal chemistry projects, we need a variety of aryl azides to construct a heterocyclic compound library. In contrast to the preparation of alkyl azides, there exist few methods for the preparation of aryl azides.[1] Generally, they can be prepared by diazotization of aryl amines and subsequent treatment with sodium azide.[4] However, sometimes, this method proves to be problematic because of compatability of functional groups. For this reason, some alternatives have been developed.[5–7] Recently, an efficient synthesis of aryl azides from the corresponding amines using triflyl azide was reported.[8] The reaction proceeds under mild conditions, normally giving high yields. One drawback of this method is that triflyl azide is not commercially available and needs to be freshly prepared. Another method for preparation of aryl azides is the Ullmann-type conversion of aryl halides using CuI as catalyst.[9] This transformation can be accelerated by addition of proline.[10] However, like some other Ullmann-type reactions,[11] the method still suffers from high reaction temperature and low reaction rate. It is known that several factors, such as ligand and solvent system, play a crucial role in the reaction rate. Careful choice of the reaction conditions should allow the reaction to proceed at relatively low temperature and in a short time. Herein we report our findings through microwave-assisted optimization of these reaction conditions, and their use for the preparation of different aryl azides from the corresponding aryl halides by conventional heating.

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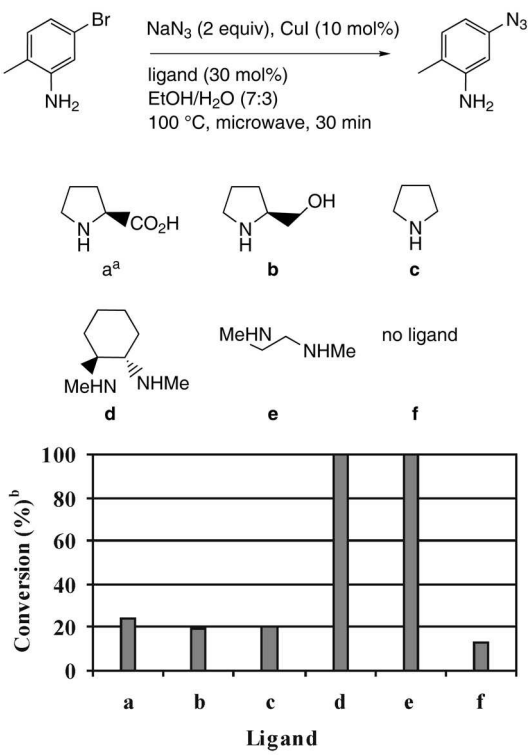
We chose 5-bromo-2-methylaniline and sodium azide as a prototype reaction to discover suitable conditions using microwave irradiation. A set of five ligands was examined for the azidonation of 5-bromo-2-methylaniline (Scheme 1). Two diamine ligands **d** and **e** efficiently accelerated this reaction. Thus, the reaction was complete in 30 minutes by using either ligand **d** or ligand **e**. Both ligands have been successfully used for other C–N bond formations.[12] Ligands **a**, **b**, and **c** proved to be less effective. Proline (**a**) did not show any substantial improvement as compared to ligands **b** and **c**. In the absence of a ligand, only 13% conversion was achieved. In the following experiments, both ligand **d** and **e** were used.



[a] 30 mol% of NaOH was used.
[b] Conversions were determined by LC-MS.

Scheme 1 Ligand screening

Next, we examined solvent systems using ligand **e**. When 1,4-dioxane was used as solvent, no conversion was observed (Table 1, entry 1). Acetonitrile proved to be fairly ineffective – only 13% conversion (Table 1, entry 2). Interestingly, in contrast to Ma's work, in which only trace

of coupling product was isolated,[10a] 55% conversion was observed when DMSO was used (Table 1, entry 3). DMSO–H_2O (5:1) gave a slightly better result (68%; Table 1, entry 4). When toluene was used, 59% conversion was observed (Table 1, entry 5). *tert*-Butanol–H_2O (2:1) turned out to be a good solvent system (73% conversion; Table 1, entry 6). However, no solvent systems tested were as good as EtOH–H_2O (7:3).

Table 1 Screening Solvent System[a]

Entry	Solvent	Conversion (%)[b]
1	1,4-Dioxane	0
2	MeCN	13
3	DMSO	55
4	DMSO–H_2O (5:1)	68
5	Toluene	59
6	*t*-BuOH–H_2O (2:19	73
7	EtOH–H_2O (7:3)	100

[a] *Reagents and conditions*: 5-bromo-2-methylaniline (1 mmol), NaN_3 (2 mmol), CuI, ligand **e**, EtOH–H_2O (7:3, 4 mL); microwave, 100 °C, 30 min.
[b] Conversions were determined by LC-MS.

We also examined catalyst and ligand loadings in this reaction. Full conversion was achieved with ligand loading down to 15% (Table 2, entry 4).

Table 2 Investigating the Loading of the Catalyst System[a]

Entry	CuI (mol%)	Ligand **e** (mol%)	Conversion (%)[b]
1	1	2	13
2	2	4	14
3	5	10	50
4	10	15	100
5	10	20	100

[a] *Reagents and conditions*: 5-bromo-2-methylaniline (1 mmol), NaN_3 (2 mmol), CuI, ligand **e**, EtOH–H_2O (7:3, 4 mL); microwave, 100 °C, 30 min.
[b] Conversions were determined by LC-MS.

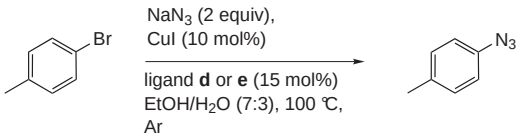
We wondered whether the fast reaction could be ascribed to the microwave effect. Therefore, the reaction times were compared using microwave irradiation and conventional heating. It turned out that conventional heating gave full conversion within 40 minutes, suggesting that the high reaction rate was not due to microwave effect. Similar reaction needs 24 hours for completion using proline as ligand.[10a]

When we tried azidonation of *p*-tolyl bromide under the optimized conditions, we observed a very high initial reaction rate (Table 3). However, after the conversion had reached 80–90% in ten minutes, the reaction rate dropped drastically (Table 3, entry 1). Increased equivalents of sodium azide, CuI, and ligand could not push the reaction to completion. All the reactions were carried out in an atmosphere of air until this point. The slow rate could be due to the deterioration of Cu(I) under air atmosphere. However, even when the reaction proceeded under argon, the same phenomenon was observed (Table 3, entry 2). We then tried another Cu(I) source,[2c] obtained from in situ reduction of $CuSO_4$ with excess sodium ascorbate. Using this Cu(I) source, azidonation of *p*-tolyl bromide was complete within 40 minutes (Table 3, entry 3). We speculated that excess of sodium ascorbate had some positive effect on the catalyst stability.[13] Indeed, as we retried the reaction by using CuI, ligand **e**, and, additionally, five mol% of sodium ascorbate, total conversion was observed in 45 minutes (Table 3, entry 4). By using ligand **d**, the reaction time was even shorter (10 min) for full conversion (Table 3, entry 5).

We also performed the reaction under the same conditions, but without ligand. It turned out that a large portion of starting material was still left after several hours. This experiment rules out the accelerating effect of ascorbate.

To lower the reaction temperature to the boiling point of the solvent system, we tried the azidonation under reflux. The reaction could be complete within ten minutes (Figure 1 and Table 3, entry 6). The reaction conditions thus far developed include reflux of an aryl bromide (2 mmol), sodium azide (4 mmol), CuI (10 mol%), sodium ascorbate (5 mol%), and ligand **d** (15 mol%) in EtOH–H_2O (7:3, 4 mL). A quantitative comparison of reactions with and without sodium ascorbate under these conditions is outlined in Figure 1 and show that ascorbate is essential for 100% conversion.

Table 3 Investigationg the Effect of Cu(I) Source and Sodium Ascorbate on the Azidonation of *p*-Tolyl Bromide



Entry	Cu source	Ligand	Sodium ascorbate (mol%)	Time (min)	Conversion (%)[a]
1[b]	CuI	**e**	–	>60	90
2	CuI	**e**	–	45	92
3	$CuSO_4$	**e**	20	40	100
4	CuI	**e**	5	45	100
5	CuI	**d**	5	10	100
6[c]	CuI	**d**	5	10	100

[a] Conversions were determined by ^1H NMR.
[b] The reaction was performed in an atmosphere of air.
[c] The reaction was carried out under reflux.

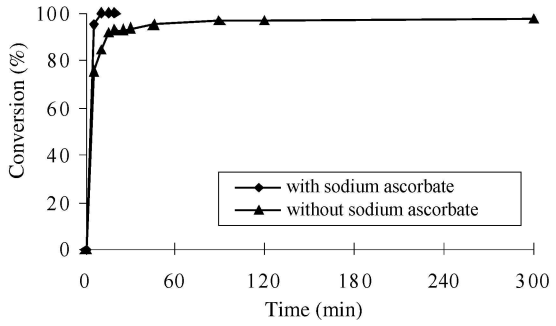


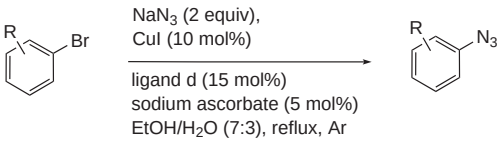
Figure 1 The effect of sodium ascorbate on the conversion of *p*-tolyl bromide (both reactions were performed under an argon atmosphere and the conversion was determined by H^1 NMR)

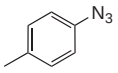
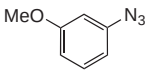
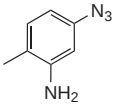
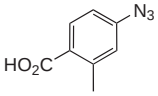
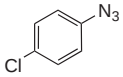
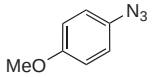
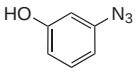
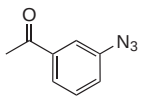
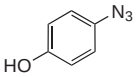
This promising result encouraged us to explore the generality of this reaction. The results are provided in Table 4. Azidonation of a wide variety of aryl bromides, presenting an assortment of functional groups, was conducted. The reactions were generally fast and complete within one hour. As previous reported, the reaction tolerates a variety of common functional groups. Thus, aryl bromides containing a phenolic OH, carboxylic acid, chloride, ketone or an anilino NH_2, were efficiently converted to the desired products.

Finally, we explored the azidonation of aryl iodides, with the intended goal to carry out this reaction at room temperature. Our first azidonation of *p*-tolyl iodide was not promising and the reaction was not complete after several hours. When we changed the solvent system from EtOH–H_2O (7:3) to DMSO–H_2O (5:1) to increase the solubility of reaction material, we observed a total conversion in 15 minutes (Table 5, entry 1). Several other phenyl azides were obtained in good to excellent yield. Prolonged reaction is prone to decompose 2-azidobenzoic acid, giving a low yield according to the literature.[1] But, by using our standard method, 2-azidobenzoic acid was obtained in 84% yield (Table 5, entry 5). For the azidonation of 3-bromo-iodobenzene (Table 5, entry 7), only 1.05 equivalents of sodium azide was used to circumvent the chemoselectivity problem because azidonation of phenyl bromides could be performed under the used conditions, albeit with a low reaction rate.

In conclusion, through optimizing the reaction conditions, a remarkably fast reaction for the azidonation of aryl halides catalyzed by Cu(I)/diamine was achieved under extremely mild conditions. We also found that the addition of sodium ascorbate has a stabilizing effect on the catalyst. In addition, we have showed that microwave is a powerful tool to optimize reaction conditions though it turned out that the reaction can be complete in the same time period under conventional heating.

Table 4 The Reaction of Aryl Bromides with Sodium Azide Using Ligand **d**



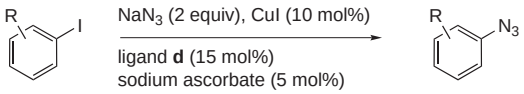
Entry	Product	Time (min)	Yield (%)[a]
1		10	89
2		40	95
3		30	99
4		20	96
5[b]		60	82
6		20	84
7		20	90
8		30	99
9		30	88
10		40	99

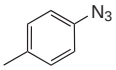
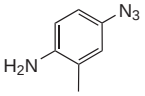
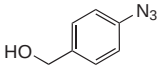
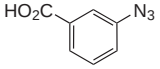
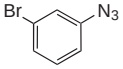
[a] Isolated yields.
[b] 1 Equiv of NaOH was used.

General Procedure for Table 4

Aryl bromide (2 mmol), NaN_3 (4 mmol), sodium ascorbate (0.1 mmol), CuI (0.2 mmol), ligand **d** (0.3 mmol), and 4 mL EtOH–H_2O (7:3) were introduced into a two-necked round-bottom flask equipped with a stirring bar and a reflux condenser. After it was degassed, and then introduced under an argon atmosphere, the reaction mixture was stirred under reflux and the progress of the reaction was followed by TLC. When the aryl bromide was completely consumed, or when the progress of the reaction had stopped, the reaction mixture was allowed to cool down to r.t., and the crude mixture was purified either by extraction and/or flash chromatography, giving the desired aryl azide.

Table 5 The Reaction of Aryl Iodides with Sodium Azide Using Ligand **d**



Entry	Product	Time (min)	Yield (%)[a]
1		15	91
2		50	99
3		35	99
4[b]		60	99
5[b]		60	84
6		120	77
7[c]		30	77

[a] Isolated yields.
[b] 1 Equiv of NaOH was used.
[c] 1.05 Equiv sodium azide was used.

General Procedure for Table 5

Aryl iodide (2 mmol), NaN_3 (4 mmol), sodium ascorbate (0.1 mmol), CuI (0.2 mmol), ligand **d** (0.3 mmol) and 4 mL DMSO–H_2O (5:1) were introduced into a two-necked round-bottom flask equipped with a stirring bar. After it was degassed, and then introduced under an argon atmosphere, the reaction mixture was stirred at r.t., and the progress of the reaction was followed by TLC. When the aryl iodide was completely consumed, or when the progress of the reaction had stopped, the crude reaction mixture was taken up in a mixture of brine and EtOAc. The aqueous phase was extracted with EtOAc (1–3 times). The combined organic phases were concentrated in vacuo, and the residue was purified by filtration through a short column of silica gel, giving the desired aryl azide.

5-Azido-2-methylbenzeneamine (Table 4, Entry 3)

Yield 99%; brown solid; mp 68–71 °C; R_f = 0.45 (PE–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.99 (d, *J* = 8.01 Hz, 1 H), 6.39 (dd, *J* = 8.01, 2.29 Hz, 1 H), 6.30 (d, *J* = 2.29 Hz, 1 H), 3.66 (br s, 2 H), 2.12 (s, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 145.8, 138.6, 131.5, 119.1, 108.9, 105.1, 16.8. HRMS (EI): *m/z* calcd for $C_7H_7N_4$ [M^+]: 148.0749; found: 148.0740. IR (FTIR-ATR): 2110 cm^{-1}.

4-Azido-2-methylbenzoic Acid (Table 4, Entry 5)

Yield 82%; white solid; mp 159–162 °C; R_f = 0.28 (PE–EtOAc, 20:1 + 1% HOAc). ^{1}H NMR (300 MHz, DMSO): δ = 12.78 (br s, 1 H), 7.88 (dd, *J* = 7.63, 1.15 Hz, 1 H), 7.05–6.99 (m, 2 H), 2.53 (s, 3 H). ^{13}C NMR (75.4 MHz, DMSO): δ = 167.7, 142.6, 141.8, 132.4, 126.7, 121.6, 116.4, 21.2. MS (EI+): *m/z* calcd for $C_8H_7N_3O_2$ [M^+]: 177; found (%): 177 (52), 149 (100) [$M^+ - N_2$]. IR (FTIR-ATR): 2109 cm^{-1}.

3-Azidophenol (Table 4, Entry 8)*[14]

Yield 99%; brown oil; R_f = 0.20 (PE–EtOAc, 10:1). ^{1}H NMR (300 MHz, DMSO): δ = 9.74 (s, 1 H), 7.19 (t, *J* = 8.01 Hz, 1 H), 6.60 (ddd, *J* = 8.01, 2.29, 0.76 Hz, 1 H), 6.54 (ddd, *J* = 8.01, 2.29, 0.76 Hz, 1 H), 6.48 (t, *J* = 2.29 Hz, 1 H). ^{13}C NMR (75.4 MHz, DMSO): δ = 158.7, 140.2, 130.7, 112.4, 109.6, 105.7. HRMS (EI): *m/z* calcd for $C_6H_5N_3O$ [M^+]: 135.0433; found: 135.0417. IR (FTIR-ATR): 2107 cm^{-1}.

* No NMR data available in the literature.

4-Azido-2-methylbenzeneamine (Table 5, Entry 2)*[15]

Yield 99%, thick brown oil; R_f = 0.19 (PE–EtOAc, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76–6.61 (m, 3 H), 3.56 (br s, 2 H), 2.15 (s, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 142.0, 130.0, 124.0, 121.0, 117.6, 116.0, 17.4. MS (EI+): *m/z* calcd for $C_7H_8N_5$ [M^+]: 148; found (%): 148 (100). IR (FTIR-ATR): 2102 cm^{-1}.

* No NMR data available in the literature.

3-Azido-1-bromobenzene (Table 5, Entry 7)*[16]

Yield 77%; yellow oil; R_f = 0.39 (PE). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (dt, *J* = 7.63, 1.15 Hz, 1 H), 7.22 (d, *J* = 7.63 Hz, 1 H), 7.18 (t, *J* = 1.15 Hz, 1 H), 6.96 (dt, *J* = 7.63, 1.15 Hz, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 141.6, 130.9, 128.0, 123.3, 122.2, 117.8. GC-MS (EI+): *m/z* calcd for $C_6H_4BrN_3$ [M^+]: 197; found (%): 90 (100) [$M^+ - N_2 - Br$]; no [M^+] found. IR (FTIR-ATR): 2133, 2098 cm^{-1}.

* No NMR data available in the literature.

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