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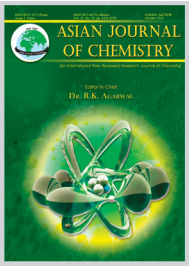

Cross-Coupling of Phenyl Halides with Sodium Dicyanomethanide in the Presence of *Tetrakis*(triphenyphosphine)palladium

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1-Aromatic substituted imidazoles were synthesized by a convenient modified process. A cross-coupling reaction of phenyl halides with sodium dicyanomethanide has been achieved to produce the arylmalononitriles coupling products as zwitterionic precursors in high yields by using catalytic *tetrakis*(triphenyphosphine)palladium under mild conditions. The molecular structure was characterized by ^{1}H NMR and ^{13}C NMR spectra, LC-MS and GC-MS. It was found that the products can be easily separated with high yields. When electron-withdrawing groups were employed, substituted phenyl bromide can also be used as the precursors to produce good yield of 87 %. This provides an efficient and practical strategy for the preparation of substituted terminal phenyl malononitriles.

Key Words: Substituted phenyl malononitriles, Zwitterionic precursors, *Tetrakis*(triphenyphosphine)palladium, Sodium dicyanomethanide.

INTRODUCTION

Arylmalononitriles are important intermediates for the synthesis of useful organic functional compounds like bioactive materials[1], organic conducting materials[2] and heterocyclic compounds in the development of new drugs[3]. They are also useful precursors of zwitterions for novel nonlinear optical materials[4].

The zwitterionic precursors can be derived from synthetically elaborated arylmalononitriles. Although many researches have reported the preparation ways of the arylmalononitriles with palladium catalyst, yet most of them need rigorous conditions such as aryl iodides[5], two different organometallic complexes as catalysts[6] and ionic liquids[7] as solvents to produce high yields. Recently, one of the conventional methods for preparation of arylmalononitriles with aryl halides and sodium dicyanomethanide followed by protonation in presence of single *tetrakis*(triphenyphosphine)palladium(0) has been presented in good yields[2a,4a]. However, this method requires proper aromatic heterocyclic compounds used as precursor to achieve good yields. In addition, the coupling reation of substituted terminal phenyl bromide with sodium dicyanomethanide for this method is even less common and the yield is not satisfied[8,9].

In the present paper, cross-coupling of phenyl halides with sodium dicyanomethanide was carried out in the presence of single *tetrakis*(triphenyphosphine)palladium catalyst. The effects of type of halides and electron-withdrawing groups, steric hindrance on the activity to the reaction were investigated.

EXPERIMENTAL

4-Bromoaniline, 4-iodoaniline, 4-iodobenzene, aniline and 1,2-dimethoxyethane were purchased from the Sinopharm Chemical Reagent Co., Ltd. 2,6-Dimethylaniline and 2,3-butanedione were purchased from Alfa Aesar. 4-Bromostyrene was purchased from Acros. *Tetrakis*(triphenyphosphine) palladium(0) was obtained from Shanxi Kaida Chemical Engineering Co. Ltd. 1,2-Dimethoxyethane was dried with anhydrous calcium dichloride, refluxed with sodium, then distilled before used. All other chemicals used in this study were commercially available and were used without further purification.

Preparation of 1-arylimidazoles: The substituted aniline (0.1 mol) in methanol (50 mL) was treated with 30 % aqueous glyoxal (16.2 mL, 0.1 mol) or 2,3-butanedione for 16 h at room temperature until a yellowish precipitate was formed. NH_4Cl (10.7 g, 0.2 mol) was added followed by 37 % aqueous aldehyde (16 mL, 0.2 mol). The mixture was diluted with

methanol (400 mL) and the resulting mixture was refluxed for 1 h. Phosphoric acid (14 mL, 85 %) was added over a period of 15 min. The resulting mixture was then stirred at reflux for additional 4-8 h. The reaction was monitored by thin layer chromatography. After removal of the solvent, the dark residue was poured onto ice (300 g) and neutralized with KOH until pH 9. The resulting mixture was extracted with dichloromethane (4 × 200 mL). The organic phases were combined and washed with water, brine and dried (Na_2SO_4). The solvent was removed and the resulting residue was chromatographed on silica gel (petroleum-EtOAc) to give the products.

The spectral data for the desired product in entries 3, 4 and 5 of Table-1. Entry 3: white solid, ^{1}H NMR (Bruker DMX 300 MHz, $CDCl_3$, TMS): δ 7.25-7.33 (m, 4H), 7.61-7.64 (d, *J* = 8.7 Hz, 2H), 7.98 (s, 1H); ^{13}C NMR (Bruker DMX 300 MHz, $CDCl_3$, TMS): δ 118.2, 121.2, 123.0, 130.1, 133.1, 135.4, 136.2.

Entry 4: white solid; ^{1}H NMR (Bruker AVA NCE III 400 Hz, $CDCl_3$, TMS) δ 7.15-7.17 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 1H), 7.25 (s, 1H), 7.79-7.81 (d, *J* = 8.8 Hz, 2H), 7.83 (s, 1H).

Entry 5: white solid, ^{1}H NMR (Bruker AVA 500 MHz, $CDCl_3$, TMS): δ 3.85 (s, 3H), 6.98-7.00 (d, *J* = 9.0 Hz, 2H), 7.19-7.21 (d, *J* = 7.5 Hz, 2H), 7.30-7.31(d, *J* = 9.0 Hz, 2H), 7.78 (s, 1H).

Preparation of arylmalononitriles: A solution of malononitrile in anhydrous 1,2-dimethoxyethane was added portionwise *via* syringe to an ice-cooled suspension of sodium hydride in anhydrous 1,2-dimethoxyethane and the mixture was stirred for 1 h at room temperature under nitrogen. Next, substituted phenyl halides and *tetrakis*(triphenyphosphine) palladium(0) (10 mol % of aryl halides) were added to the above resulting pink suspension under an N_2 flow. The reaction mixture was stirred and refluxed under N_2 for 2-5 h. After cooling to room temperature, the solvent was then removed under reduced pressure from the reaction mixture. The resulting solid was washed with benzene to eliminate the catalyst, dissolved in water and filtered to give a dark-yellow aqueous solution. The solution was neutralized with 5 % HCl to pH = 7 and the resulting yellow precipitate was collected by filtration to give an orange solid without further purification in entry 1 and 2 of Table-2. The purity of arylmalononitriles is > 93 %. In entry 3 and 4, the reaction mixture was poured into cool water, neutralized with 10 % HCl and extracted with CH_2Cl_2. Then, the organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The crude product was detected by GC-MS.

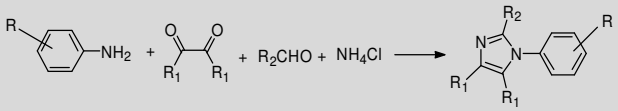
The spectral data for the desired product in entry 1 and 2 of Table-2: yellow solid, ^{1}H NMR (Bruker AVA NCE III 400 Hz, DMSO-d_6, TMS): δ 4.501 (s, 1H), 6.840-6.861 (δ, *J* = 8.4 Hz, 2H), 7.398-7.420 (d, *J* = 8.8 Hz, 2H), 7.837 (s, 1H), 8.127 (s, 1H), 9.492 (s, 1H); ^{13}C NMR (Bruker AVA NCE III 400 Hz, DMSO-d_6, TMS): δ 29.079, 118.102, 120.597, 121.507, 122.114, 124.806, 128.835, 133.415, 143.703; MS, m/z: 209.1 (M+1), 145.1 (M+1).

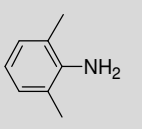
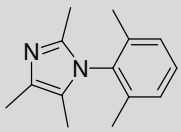
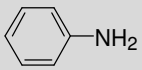
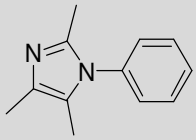
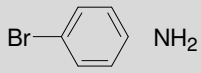
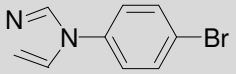
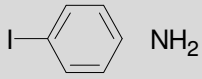
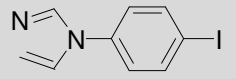
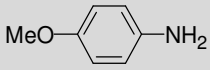
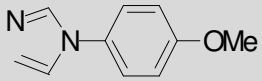
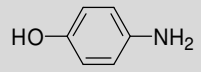
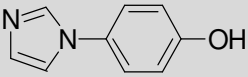
Detection method: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVA 500 MHz, Bruker AVA NCE III 400 Hz and Bruker DMX 300 MHz. LC-MS was performed using Agilent technologies 1200 seris and Agilent technologies 6130 seris. GC-MS was measured by Agilent 5973.

RESULTS AND DISCUSSION

The synthesis of the 1-arylimidazoles follows a slightly modified protocol adapted from Zhang *et al.*[10b] and Strassner *et al.*[10a]. The substituted aniline, glyoxal or 2,3-butanedione and aldehyde are converted into 1-arylimidazoles in a onepot reaction. As it is seen from Table-1, the yield of 1-arylimidazoles was relatively low when sterically hindered 1-aromatic substituted imidazoles were used (Table-1, entries 1 and 2). The low yield for entry 7 can be explained by its solubility in water, so the extraction of the product is the limiting factor.

TABLE-1
PREPARATION OF 1-ARYLIMIDAZOLES FROM SUBSTITUTED ANILINE



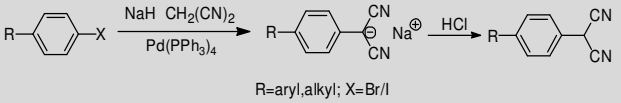
Entry	RNH_2	Product	Yield (%)
1			21[a]
2			45[a]
3			61
4			68
5			80
6			4[a]

[a]Yields based on GC analysis

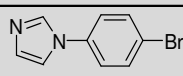
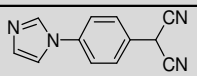
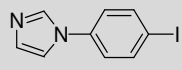
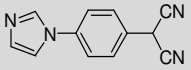
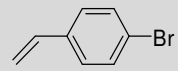
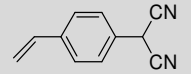
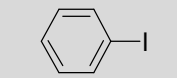
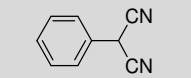
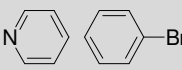
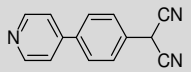
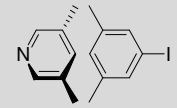
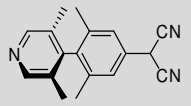
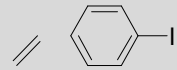
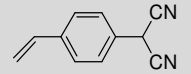
As described in Table-2, the reactivity of the halides was in the normal order: I > Br through comparing entries 1, 3, 5 to 2, 7 and 6 and electron-withdrawing groups also affected this reaction. The yield was improved when electron-withdrawing groups were employed. Compared with entry 1, the entry 5 with sodium dicyanomethanide only provided the product in 38 % yield while the yield of entry 1 was 87 %. The reason for increase of the yield can be ascribed to stronger electron deficiency of the imidazole ring in entry 1 than that of pyridine ring in entry 5. The same result can be obtained from entries 4 and 7. The vinyl should be more electron deficiency than hydrogen atom. Similarly, when it comes to entries 3, 7 and 1, 2, the yields rise from 0 to 87 % and 72 % to 94 % respectively, because imidazole ring is more electron deficiency than vinyl. Under the same conditions described in

Table-2, the cross coupling of entry 6 and sodium dicyanomethanide efficiently proceeded to give higher yield than entry 2. It seems that the steric hindrance is favourable to the reaction.

TABLE-2
Pd(PPh3)4-CATALYZED SYNTHESIS OF ARYLMALONONITRILES



R=aryl,alkyl; X=Br/I

Entry	Compad.	Product	T (h)	Yield (%)
1			5	87
2			5	94
3			5	0
4			2	0
5			Overnight	38[a]
6			5	96[b]
7			2	72[b]

a. Ref. 9. b. Ref. 4g.

Conclusion

In summary, a new and facile approach is developed for the synthesis of terminal phenyl malononitriles. Through *tetrakis*(triphenyphosphine)palladium(0) catalyzed coupling reaction, we can get the final product in high yield. Moreover the experimental procedure is simple and easy to control; therefore, the reaction would be suitable for many other substituted terminal phenyl malononitriles syntheses.

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