Tetrahedron Letters 50 (2009) 5505–5509

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of biaryl pentacyclic quinolonoquinoxalino-oxazocines in aqueous medium using Amberlite IRA 402(OH)

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ARTICLE INFO

Article history:
Received 30 June 2009
Revised 14 July 2009
Accepted 16 July 2009
Available online 21 July 2009

Keywords:
Amberlite IRA 402(OH)
Pentacyclic quinolonoquinoxalino-oxazocine
Biaryl quinolone

ABSTRACT

Amberlite IRA 402(OH) effectively mediates biarylation via Suzuki–Miyaura cross-coupling reaction on complex systems such as dihalo quinolonoquinoxalino-oxazocines.

1. Introduction

Green chemistry has become a major field of interest for the community of chemists trying to overcome the challenges of the environmental legislation, which is coming into effect all over the world[1] and has encouraged the development of cleaner chemical processes and new technologies.[2] Most chemical reactions that contribute adversely toward the environment are multi-step reactions which (a) involve protection and deprotection steps, (b) use hazardous solvents and stoichiometric reagents, and (c) lack atom-economy and effective energy source.[3] To overcome these problems concerted efforts have been made for the development of efficient methodologies. A number of reports have appeared in the literature where water has been used as solvent, microwave irradiation as alternative energy resource, and metal-catalyzed coupling reactions as convenient one-step methods for assembling complex structures.[4] Among them, palladium-catalyzed Suzuki–Miyaura coupling reaction of aryl halides with aryl boronic acids is a powerful tool for the synthesis of biaryl derivatives,[5] which are found in a range of pharmaceuticals, herbicides, and natural products.[6] In a recent communication we have disclosed the synthesis of biaryl derivatives of fused tricyclic oxa-aza-quinolones applying the basics of Suzuki–Miyaura reaction using basic alumina as solid support.[7] However, this methodology has some limitations: debromination occurred when it was applied to more complex systems. We were therefore compelled to find an alternative for basic alumina for the synthesis of biaryl derivatives of fused pentacyclic quinolonoquinoxalino-oxazocines, which are structurally similar to anti-carcinogenic pentacyclic heteroaromatics[8] and were recently synthesized by our group.[9] In this Letter, we wish to disclose the progression of overcoming the problem of biarylation on complex systems such as pentacyclic quinolonoquinoxalino-oxazocines.

At the outset, we chose 5,7-dibromoquinolonoquinoxalino-oxazocine (**1a**) and *p*-methoxy phenyl boronic acid (**2b**) as model reaction partners to evaluate the various catalytic conditions. It was revealed from the systematic studies that the reactions catalyzed by $Pd(OAc)_2/PPh_3$ in CH_3CN using bases such as KF, K_3PO_4, and even Cs_2CO_3 were ineffective, and only low yield was obtained with Na_2CO_3. Similar reactions performed in solvents such as dioxane, toluene, DCE, and DMSO under otherwise identical conditions were also found to be totally ineffective, though in DMF low to moderate yield was obtained. Next we attempted the reaction in DMF with $PdCl_2/PPh_3$ or $PdCl_2(PPh_3)_2$ as catalyst and Na_2CO_3 as base; this yielded the desired biaryl product though with only 20–30% yield. Interestingly, reaction using Na_2CO_3 and $Pd(PPh_3)_4$ produced moderate yield (40–50%) of the product. We then explored our optimization protocol with $Pd(PPh_3)_4$ in aqueous medium in presence of different inorganic bases; moderate yield (60%) was obtained in presence of Na_2CO_3 in 16 h (Table 1, entry 8). Taking into account the efficacy of the catalytic system $Pd(PPh_3)_4/H_2O$, the study was further explored using an ion-exchange resin, as base. Since, in recent years, ion-exchange resins have been increasingly utilized in differ-

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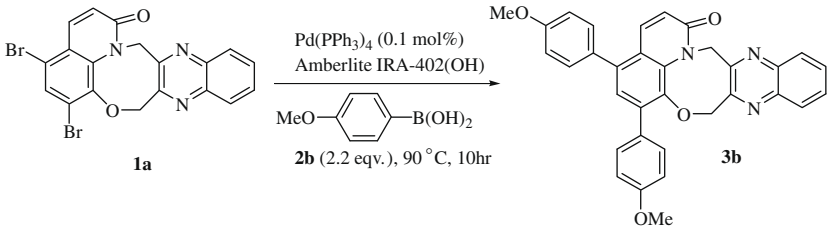
doi:10.1016/j.tetlet.2009.07.072

Table 1
Optimization of Suzuki–Miyaura cross-coupling reaction using dibromo-quinolonoquinoxalino-oxazocine (**1a**) and *p*-methoxy benzene boronic acid (**2b**) in aqueous medium[a]



Entry	Base/resin	$Pd(PPh_3)_4$ (mol %)	Time (h)	*T* (°C)	Yield[b] (%)
1	Cs_2CO_3	0.5	12	90	NR
2	Cs_2CO_3	1.0	16	120	NR
3	Cs_2CO_3	2.0	16	120	NR
4	KF	0.1	12	120	NR
5	KF	0.5	16	120	NR
6	KF	2.0	16	120	NR
7	Na_2CO_3	0.1	12	110	50
8	Na_2CO_3	0.5	16	120	60
9	Na_2CO_3	1.0	24	130	60
10	K_3PO_4	0.5	12	120	NR[c]
11	K_3PO_4	1.0	16	120	NR
12	K_3PO_4	2.0	16	130	NR
13	Amberlite IRA-402(OH)	0.5	12	80	90
14	Amberlite IRA-402(OH)[d]	0.5	10	90	95
15	Amberlite IRA-402(OH)	1.0	10	90	95
16	Amberlite IRA-402(OH)	0.1	10	90	95
17	Amberlite IRA-402(OH)	0.05	10	90	70

[a] All the studies were performed by using **1a** and **2b** under classical heating condition and in an inert atmosphere.
[b] Isolated yield.
[c] No reaction.
[d] Resin (400 mg) was found to be sufficient for quantitative yield of biaryl product; lesser amount resulted in low yield.

ent areas of organic synthesis including C–C coupling reactions such as Heck and Sonogashira reaction.[10] It is an inexpensive, commercially available, environmentally compatible solid basic catalyst used as reagent support and in chemical processing.[11]

To our satisfaction, the reaction catalyzed by $Pd(PPh_3)_4$ in H_2O at 90 °C in presence of Amberlite IRA 402(OH) proved to be the best with respect to both the yield of the product and the reaction time (Table 1, entries 14–16). It is notable that 0.1 mol % catalyst loading was enough to produce almost quantitative yield; no significant effect on the yield of the product was observed on enhancement of catalyst loading from 0.1 to 1 mol %. With an optimal set of catalytic conditions thus selected, we then extended the Suzuki–Miyaura cross-coupling reaction of **1a**/**b** with a number of aryl/heteroaryl boronic acid derivatives (**2a–j**). This demonstrated that the method constitutes an effective biarylation protocol with 85–96% yield (Table 2). Comparison of the coupling reactivity of various aryl boronic acids, summarized in Table 2, indicates that electron-donating substituents (–OMe, –Me) *para* to the boronic acid could assist the reactivity and thus afford higher yield of biaryl quinolones (Table 2, entries 2, 3, and 10) within 10–12 h. Similarly, coupling of furan-2-boronic acid with **1a** afforded the target product in 92% yield in 12 h (Table 2, entry 6). Nitrogen and sulfur containing heteroaryl boronic acids (thiophen-3-boronic acid and pyridine-3-boronic acid) also showed high reactivity and assured good to high yield (Table 2, entries 7 and 11). Naphthalene-1-boronic acid gave the desired product in 85% yield (Table 2, entry 9), while naphthalene-2-boronic acid furnished 95% yield under the standard reaction conditions (Table 2, entry 8); the lower yield in the former case may be due to steric hindrance offered by the fused ring. All the products were characterized by their MS, ^1H, and ^{13}C NMR spectroscopy.[12] Single crystal X-ray crystallographic analysis of biaryl derivative **3a** was carried out for unambiguous determination of its structure (Fig. 1).

The plausible pathway of the reaction is outlined in Scheme 1. It is presumed that the reaction is initiated with the Amberlite resin (**III**) transforming the oxidative addition product **II** to produce the intermediate **V**, while aryl boronic acid (**2**) gets converted to intermediate **VI**. The migration of Ar_1 from **VI** to **V** produces intermediate **VIII** with liberation of quaternary ammonium borate **VII**.

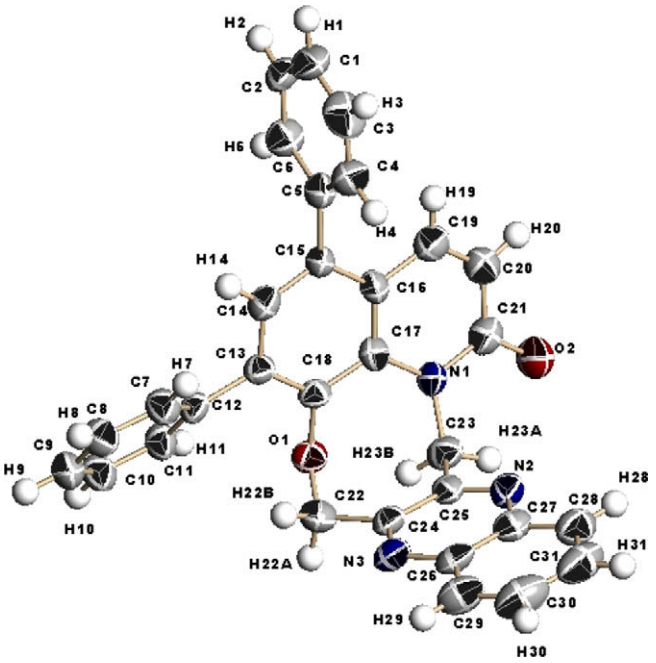
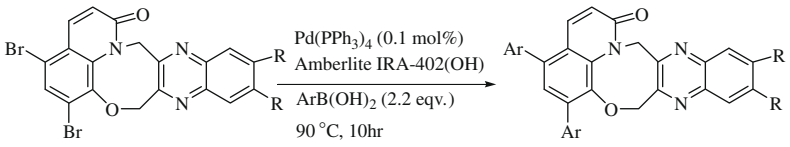


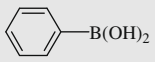
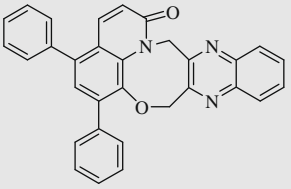
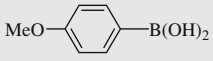
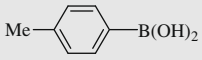
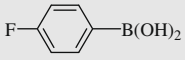
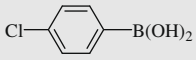
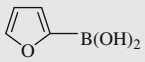
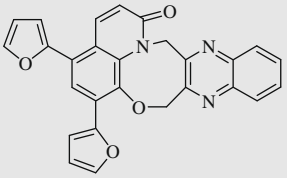
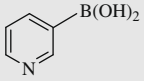
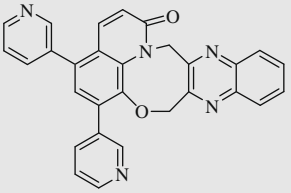
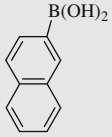
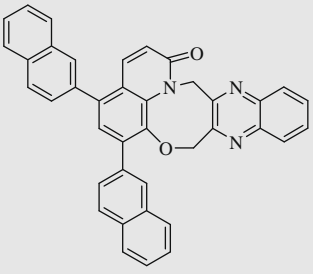
Figure 1. ORTEP representation of compound **3a**, the displacement ellipsoid is drawn at a probability of 50%.

Table 2
Construction of biaryl quinolono quinoxaline motifs from dibromoquinolono quinoxaline (**1a–b**) and boronic acid (**2a–i**) substrates



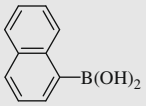
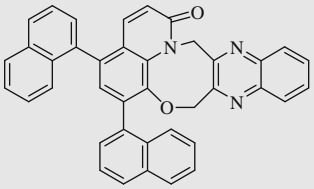
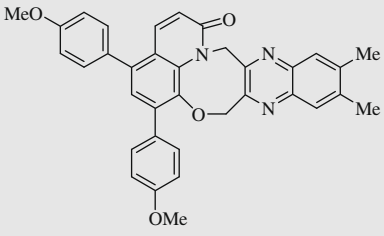
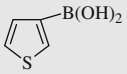
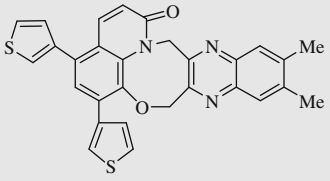
1a; R = H
1b; R = Me

3(a-i); R = H
3(j-k); R = Me

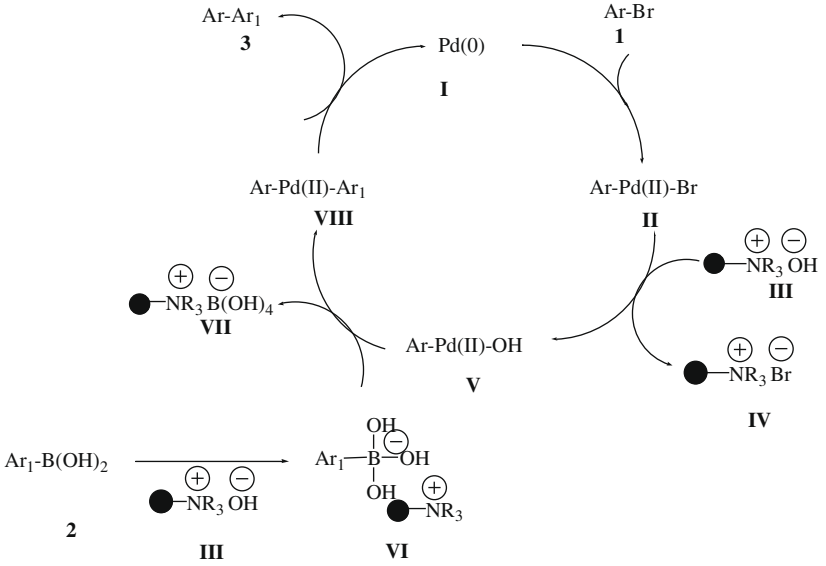
Entry	Aryl bromide (**1a–b**)	Boronic acid (**2a–j**)	Product[a] (**3a–k**)	Time (h)	Yield[b] (%)
1	**1a**	 **2a**	 **3a**	12	90
2	**1a**	 **2b**	**3b**	10	95
3	**1a**	 **2c**	**3c**	10	92
4	**1a**	 **2d**	**3d**	12	90
5	**1a**	 **2e**	**3e**	12	85
6	**1a**	 **2f**	 **3f**	12	92
7	**1a**	 **2g**	 **3g**	10	90
8	**1a**	 **2h**	 **3h**	12	95

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl bromide (**1a–b**)	Boronic acid (**2a–j**)	Product[a] (**3a–k**)	Time (h)	Yield[b] (%)
9	**1a**	 **2i**	 **3i**	12	85
10	**1b**	**2b**	 **3j**	10	95
11	**1b**	 **2j**	 **3k**	12	92

[a] All the new products were characterized by mass, ^{1}H and ^{13}C NMR spectral analysis.
[b] Isolated yield.



Scheme 1. Mechanistic pathway for Amberlite IRA-402(OH) mediated Suzuki–Miyaura cross-coupling reaction.

Quaternary ammonium salt **IV** then effects the conversion of **VIII** [Pd(II)] to **I** [Pd(0)],[13] stabilizing the palladium catalyst leading to the acceleration of Suzuki reaction. In the absence of the resin the reaction did not yield the desired product even after 24 h. Generalization of this methodology was then ensured by performing reactions on simpler aryl bromides with different aryl boronic acids and this also resulted in comparable yields.[4d] To the best of our knowledge this is the first report of Amberlite IRA 402(OH) mediated Suzuki–Miyaura cross-coupling reaction.

The reusability of the resin was then investigated because it is very important for industrial and pharmaceutical applications. After work-up of the reaction, the resin was recovered by simple filtration, washing with ethanol followed by sodium hydroxide solution, and drying at 80 °C under reduced pressure. Even after

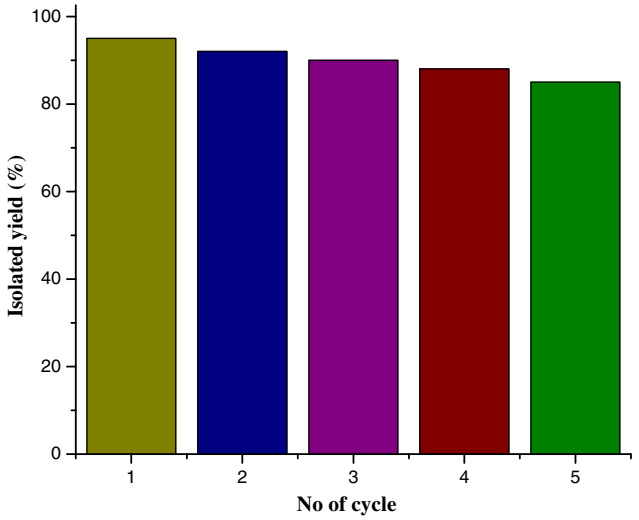


Figure 2. Reusability of the Amberlite IRA 402(OH) resin tested using **1a** and **2b**.

consecutive five-time use of the resin, there is only a slight decrease in the conversion (95–85%) of the biaryl products (Fig. 2).

2. Conclusion

In summary, we have described a simple, convenient, and efficient protocol for the preparation of biaryl quinolonoquinoxalino-oxazocines from 5,7-dibromoquinolono quinoxalino-oxazocines using Amberlite IRA 402(OH) ion-exchange resin. The attractiveness of this protocol lies in the mild reaction conditions, greater selectivity, simplicity in operation, cleaner reaction profiles, and low cost coupled with reusability of the resin. These make it an attractive green process for the synthesis of biaryl heteroaromatics of biological importance.

Acknowledgments

We like to thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support in the form of fellowships to P. Paira, R. Paira, A. Hazra, K. B. Sahu, S. Naskar, P. Saha, S. Mondal and A. Maity, Mr. K. K. Sarkar for HRMS analysis and Mr. Rajendra Mahato for technical help. We are also thankful to Dr. B. Achari, Emeritus Scientist, CSIR, for critical suggestions and encouragement.

Supplementary data

Supplementary data (Experimental procedures, characterization for all compounds and crystallographic data.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.072.

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11. http://www.sigmaaldrich.com/chemistry/aldrich-chemistry/tech-bulletins/al-142/amberlite-amberlyst.html.
12. *General reaction procedure for the synthesis of biaryl quinolones* (**3a–k**): Appropriate amount of dihaloquinolonoquinoxalino-oxazocine (**1a**/**b**) (0.5 mmol) was taken in 20 mL of water in a 100 mL RB flask under inert atmosphere, 400 mg of Amberlite IRA 402(OH) was added, and the mixture was stirred at 45–50 °C till dissolution of the substrate. Then 0.0005 mmol $Pd(PPh_3)_4$ and aryl or hetero aryl boronic acids **2a–j** (1.1 mmol, 1:2.2 molar ratio with respect to the substrate) were added to the stirred solution and the stirring was continued for 30 min. The flask was placed in an oil bath and the stirring was continued for 10–12 h at 90–95 °C. After completion of the reaction, the resin was recovered by simple filtration, thoroughly washed with ethanol followed by sodium hydroxide solution, and dried at 80 °C under reduced pressure for subsequent runs. The filtrate was transferred to a separating funnel and extracted with ethyl acetate. The organic layer was washed thoroughly with water until free from alkali, dried over anhydrous sodium sulfate, and evaporated to dryness in a rotary evaporator under reduced pressure. The residue was chromatographed over silica gel (60–120, mesh), eluting with a mixture of ethyl acetate–pet. ether in different ratios to yield the biaryl quinolones (**3a–k**).
Compound **3a**: Obtained from 20% ethyl acetate–pet. ether fraction and crystallized from chloroform–hexane mixture to give white crystalline solid in 90% yield. Mp 220 °C; R_f (60% pet. ether–chloroform) 0.55; IR (KBr, cm^{-1}) ν 3444, 1660, 1419, 767. ^1H NMR (600 MHz, $CDCl_3$): δ 4.96 (1H, d, J = 15.6 Hz), 5.49 (1H, d, J = 16.2 Hz), 6.17 (1H, d, J = 13.8 Hz), 6.53 (1H, d, J = 13.8 Hz), 6.66 (1H, d, J = 9.6 Hz), 7.22 (1H, s), 7.35 (2H, m), 7.45(4H, m), 7.51 (2H, t, J = 7.8 Hz), 7.67 (3H, m), 7.73 (2H, m), 7.91(1H, m), 8.20 (1H, m); ^{13}C NMR ($CDCl_3$, 150 MHz): δ. 50.4 (CH2), 77.2 (CH2), 120.4 (C), 121.9 (CH), 126.7 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 128.9 (C), 129.4 (2 × CH), 129.8 (CH), 129.9 (2 × CH), 130.0 (CH), 130.5 (CH), 134.7 (C), 137.0 (C), 137.2 (CH), 138.1 (C), 138.7 (C), 141.1 (C), 141.8 (C), 143.9 (C), 150.1 (C), 151.7 (C), 163.1 (C, CO). ESI-MS: m/z 468 $[M+H]^+$, 490 $[M+Na]^+$ HRMS: calcd 490.1531 $[M+Na]^+$; found 490.1537.
Compound **3h**: Obtained from 30% ethyl acetate–pet. ether fraction and crystallized from chloroform–hexane mixture to give a white crystalline solid in 95% yield. Mp 202–204 °C; R_f (60% pet. ether–chloroform) 0.52; IR (KBr, cm^{-1}) ν 3055, 3009, 1661, 1587, 754. ^1H NMR (600 MHz, $CDCl_3$): δ 4.97 (1H, d, J = 16.2 Hz), 5.49 (1H, d, J = 16.2 Hz), 6.23 (1H, d, J = 13.8 Hz), 6.59 (1H, d, J = 13.8 Hz), 6.68 (1H, d, J = 9.6 Hz), 7.43 (1H, s), 7.49 (1H, d, J = 8.4 Hz), 7.55 (4H, m), 7.72 (3H, m) 7.86 (3H, m), 7.92 (5H, m), 7.99 (1H, d, J = 8.4 Hz), 8.1 (1H, s), 8.20 (1H, m); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 50.2 (CH2), 77.2 (CH2), 120.7 (C), 122.0 (CH), 126.4 (CH), 126.5 (CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.8 (2 × CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (2 × CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 129.9 (CH), 130.5 (CH), 132.7 (C), 132.9 (C), 133.1 (C), 133.4 (C), 134.6 (C), 134.8 (C), 136.1 (C), 137.1 (C), 137.2 (CH), 138.2 (C), 141.1 (C), 141.8 (C), 144.0 (C), 150.1 (C), 151.7 (C), 163.1 (C, CO). ESI-MS: m/z 568 $[M+H]^+$, 590 $[M+Na]^+$ HRMS: calcd 590.1844 $[M+Na]^+$; found 590.1844.
13. (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) Deshmukh, R. R.; Rajagopal, R.; Srinivasan, K. V. *Chem. Commun.* **2001**, 1544.