Tetrahedron Letters 51 (2010) 1736–1738

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of benzodiazocine-annulated heterocycles by the implementation of Pd-catalyzed intramolecular Heck reaction

K. C. Majumdar *, Krishanu Ray, Sintu Ganai

Department of Chemistry, University of Kalyani, Kalyani 741 235, W.B., India

ARTICLE INFO

Article history:
Received 19 December 2009
Revised 21 January 2010
Accepted 25 January 2010
Available online 1 February 2010

Keywords:
Benzodiazocine
Heterocycles
Intramolecular Heck reaction
$Pd(OAc)_2$
$Pd(PPh_3)_4$

ABSTRACT

Syntheses of hitherto unreported benzodiazocine-annulated heterocycles by the implementation of palladium-catalyzed intramolecular Heck reaction has been achieved in excellent yields.

Medium ring heterocycles are important class of synthetic targets to the organic chemists because of their presence as structural core moiety in a large number of natural products.[1] In particular seven- and eight-membered heterocycles are constituents of a number of compounds with interesting pharmacological properties.[2,3] However, medium-sized heterocycles particularly eight-membered or higher membered are difficult to prepare due to unfavorable entropic and enthalpic factors and transannular interactions.[4] In general, the number of methods for the synthesis of medium ring heterocycles are rare in literature. Today the most powerful methodology for the construction of medium ring heterocycles is the ring closing metathesis (RCM),[5,6] that some time requires high dilution conditions for successful conversion and often involves generation of byproducts such as ethylene. Currently palladium-catalyzed intramolecular Heck reaction have attracted much interest due to their excellent functional group tolerance and high selectivity. Recently we have reported the synthesis of a variety of medium-sized heterocycles by the application of this methodology.[7] However, there are very few reports to the synthesis of eight-membered heterocycles containing two nitrogen or heteroatom. The addition of medium-sized rings containing two nitrogen atoms as substituents in biologically active compounds is known to increase the pharmaceutical potency of the compounds. One example is the diazocine ring. The tethering of octahydro-1,4-diazocines to guanidine has produced derivatives of superior anti-hypertensive activity to that of guanidine.[8] Moreover the derivatives of benzodiazocine are interesting because of their use as amoebicidal agents.[9] Polycyclic benzodiazocines of natural origin are potent inhibitors of protein kinase C and cyclic nucleotide-dependent protein kinases, used in experimental pharmacology[10] and simple benzodiazocines have been used as homologues of benzodiazepine drugs.[11]

Buchwald and his co-workers have developed[12] a procedure for the synthesis of benzodiazocine derivatives utilizing sequential Cu-catalyzed coupling of a β-lactam with bromo or iodo aryl amine, intramolecular attack of the amino group and ring expansion. Recently some other methodologies for the synthesis of pyrrolo benzodiazocines have been reported[13–15] in good yields. However, to our knowledge there is no report on the synthesis of heterocycles-annulated diazocines except pyrrole. We therefore, became interested to undertake a study on the synthesis of bioactive diazocine-annulated quinoline, coumarin and pyrimidine derivatives by the implementation of palladium catalysts under ligand free conditions.[16] Herein we report our results.

The precursors (**4–7**) required for our present study were synthesized in 85–92% yields by refluxing the chloroacylated amides **2a–d** with different tosylated bromoanilines (**3a–c**) in dry acetone for 4–5 h in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions[17]). The compounds **2a–d** were in turn prepared by subsequent treatment of chloroacetyl chloride on **1a–d** under phase transfer catalysis condition using TBAHS as catalyst and potassium carbonate as base (Scheme 1).

We first attempted palladium-catalyzed Heck reactions with these substrates (**4–7**). The first set of experiment was carried

* Corresponding author. Tel.: +91 33 2582 7521, fax: +91 33 2582 8282.
E-mail address: kcm_ku@yahoo.co.in (K.C. Majumdar).

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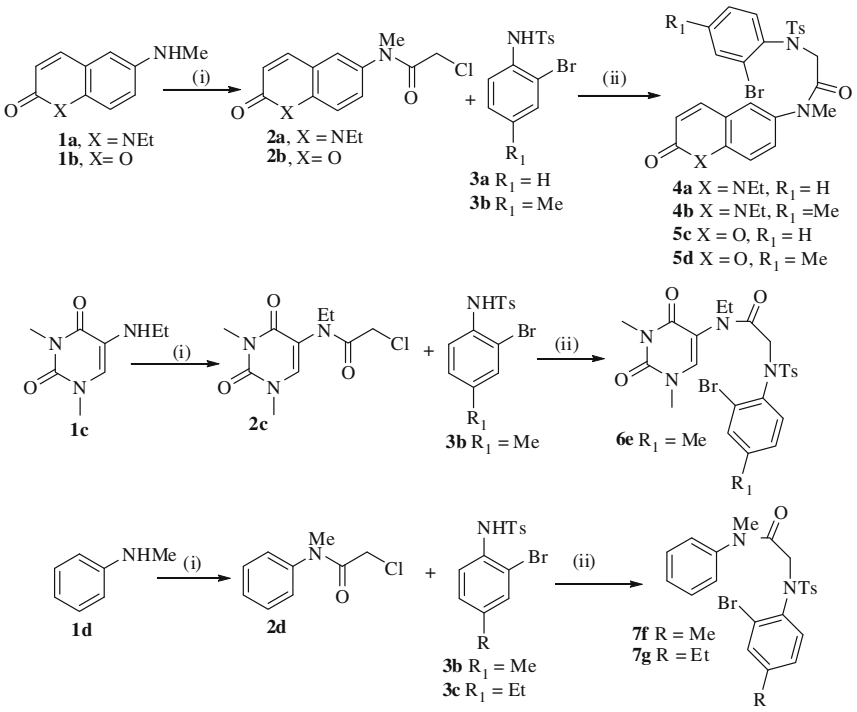
doi:10.1016/j.tetlet.2010.01.088



Scheme 1. Reagents and conditions, (i) chloroacetyl chloride, DCM–H_2O, TBAHS, K_2CO_3, rt, 0.5 h, (ii) dry acetone, K_2CO_3, NaI, reflux, 4–5 h.

out with **4a**[18] as the model substrate. Initially the reaction was performed in dry *N,N*-dimethylformamide (DMF), using 10 mol % palladium acetate, potassium acetate as base in conjunction with TBAB, for 8 h under nitrogen atmosphere at 120 °C to give the cyclized product **8a**[19] in 65% yield. Further enhancement of the temperature of the reaction or the catalyst loading (20 mol %) did not improve the yield of the reaction. However, when the same reaction was conducted by changing the catalyst, that is, replacing $Pd(OAc)_2$ with $Pd(Ph_3)_4$ keeping the other parameters unchanged the reaction was found to proceed at a relatively enhanced rate, that is, shorter reaction time (6 h) affording better yield of the cyclized product (90%). To optimize the reaction conditions we have conducted a series of experiments where changes were made in case of catalyst, base, and solvent. This study revealed that the catalyst, base and solvent have a pronounced effect on yield of the reaction. Among various bases used for the reaction, potassium acetate was found to provide the highest yield. The reaction was studied in different solvents like DMA, dioxane, toluene etc but DMF was found to be the choice (Table 1). Additive TBAB plays an important role in this reaction because in the absence of TBAB the reaction does not give any cyclized product.

Similar treatment of other substrates (**4–7**) under the above optimized condition [$Pd(Ph_3)_4$, KOAc, TBAB, DMF] gave the desired cyclized products in good to excellent yields except in the case of substrates **7f** and **7g**. These two substrates (**7f**,**g**) were found to give the products with $Pd(OAc)_2$ catalysis instead of $Pd(PPh_3)_4$ in 90–92% yields within 4 h. The results are summarized in Table 2.

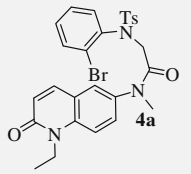
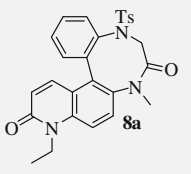
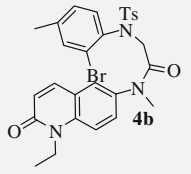
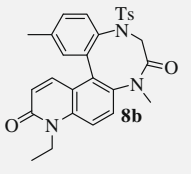
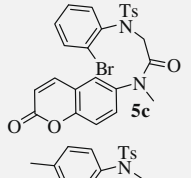
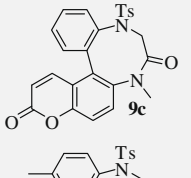
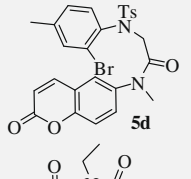
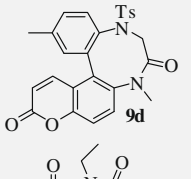
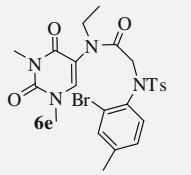
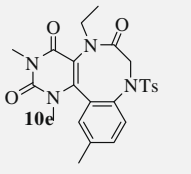
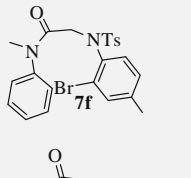
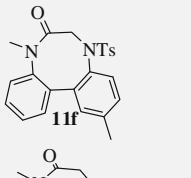
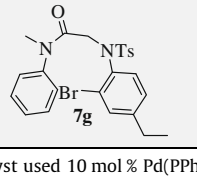
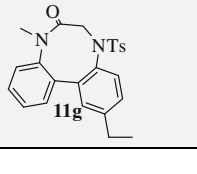
In conclusion we have developed an important synthetic protocol for the synthesis of eight-membered benzodiazocine-annulated heterocycles by Pd-catalyzed intramolecular Heck reaction as the key step. The reaction conditions are simple, straightforward and high yielding. The reaction is highly regioselective, and affords the desired medium ring heterocycles in excellent yields. Implementation of this strategy to the synthesis of heterocyclic library is under way and will be reported later.

Table 1
Optimization of the palladium-catalyzed intramolecular Heck reactions[a]

Entry	Catalyst[b]	Base[c]	Solvent	Yield[d] (%)
1	$Pd(OAc)_2$	KOAc	DMF	65
2	$Pd(OAc)_2$	K_2CO_3	DMF	<10
3	$Pd(OAc)_2$	Et_3N	DMF	NR
4	**$Pd(PPh_3)_4$**	**KOAc**	**DMF**	**90**
5	$Pd(PPh_3)_2Cl_2$	KOAc	DMF	75
6	$Pd(PPh_3)_4$	NaOAc	DMF	82
7	$Pd(OAc)_2$	KOAc	DMA	48
8	$Pd(PPh_3)_4$	KOAc	DMA	74
9	$Pd(OAc)_2$	KOAc	Toluene	NR
10	$Pd(PPh_3)_4$	KOAc	Dioxane	NR

[a] The reactions are carried out at 120 °C, TBAB was used as additive.
[b] Catalyst used 10 mol %.
[c] Base used 2.75 equiv.
[d] Yields are isolated. NR indicates no reaction.

Table 2
Summarized results of the Heck reaction[a]

Entry	Precursors	Time (h)	Products	Yields[c] (%)
1[a]	 **4a**	6	 **8a**	90
2[a]	 **4b**	6	 **8b**	88
3[a]	 **5c**	6	 **9c**	84
4[a]	 **5d**	6	 **9d**	86
5[a]	 **6e**	6	 **10e**	85
6[b]	 **7f**	4	 **11f**	90
7[b]	 **7g**	4	 **11g**	92

[a] Catalyst used 10 mol % $Pd(PPh_3)_4$.
[b] Catalyst used 10 mol % $Pd(OAc)_2$.
[c] Isolated yield of products.

Acknowledgements

We thank the DST (New Delhi) and CSIR (New Delhi) for financial assistance. Two of us (K.R. and S.G.) are grateful to the CSIR (New Delhi) for their research fellowships.

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18. *General procedure for the preparation of the Heck-precursor* ***4a****:* A mixture of the compound **2a** (300 mg, 1.07 mmol), tosylated-2-bromoaniline **3a** (421 mg, 1.29 mmol) and anhydrous K_2CO_3 (1.0 g) was refluxed in acetone (50 mL) for 4–6 h. in the presence of sodium iodide. The reaction mixture was cooled, filtered and the solvent was removed. The crude product was purified by column chromatography over silica gel (60–120 mesh) using petroleum ether–ethyl acetate (3:2) as eluent to give **4a** in 88% yield. *Compound* ***4a***: Yield: 88%, solid; mp 190–192 °C; IR(KBr): ν_{max} = 1648, 1676, 2925 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ_H = 7.73 (d, 1H, *J* = 7.7 Hz), 7.61 (d, 1H, *J* = 9.4 Hz), 7.54 (d, 2H, *J* = 7.9 Hz), 7.49 (d, 1H, *J* = 7.7 Hz), 7.42 (d, 1H, *J* = 9.1 Hz), 7.28–7.33 (m, 3H), 7.17–7.20 (m, 3H), 6.77 (d, 1H, *J* = 9.4 Hz), 4.63 (br s, 1H), 4.36 (q, 2H, *J* = 7.0 Hz), 3.89 (br s, 1H), 3.24 (s, 3H), 2.39 (s, 3H), 1.38 (t, 3H, *J* = 7.0 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 12.7, 21.5, 37.6, 37.9, 51.7, 115.8, 121.8, 123.2, 124.4, 127.2, 127.8, 128.0, 129.2, 129.3, 130.0, 133.3, 135.0, 136.3, 137.1, 137.7, 138.1, 138.6, 143.5, 161.6, 167.8 ppm. HRMS: *m*/*z* calcd for $C_{27}H_{26}BrN_3O_4S$: [M^++Na]: 590.0725, [M^++Na+2]: 592.0708; found: 590.0725, 592.0725.
19. *General procedure for the synthesis of the compound* ***8a*** *by Heck reaction*: A mixture of **4a** (100 mg, 0.17 mmol), tetrabutylammonium bromide (85.2 mg, 0.26 mmol) and anhydrous potassium acetate (41.6 mg, 0.42 mmol) was taken in *N*,*N*-dimethylformamide (DMF) (10 mL) under nitrogen atmosphere. $Pd(PPh_3)_4$ (10 mol %, 20.3 mg) was added and the reaction mixture was stirred at 120 °C for 6 h. The reaction mixture was cooled, water (20 mL) was added and extracted with ethyl acetate (3 × 30 mL). The ethyl acetate extract was washed with water (2 × 40 mL), followed by brine (30 mL). The organic layer was dried (Na_2SO_4), and the solvent was evaporated to give a crude product. This was purified by column chromatography over silica gel (230–400 mesh) using petroleum ether and ethyl acetate (3:2) as an eluent. The product **8a** was isolated as a white solid in 90% yield. Similarly the other compounds **8b**–**11g** were prepared in 84–92% yields. *Compound* ***8a***: Yield: 90%, solid; mp 216–218 °C; IR(KBr): ν_{max} = 1656, 1680, 2925 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.98 (d, 1H, *J* = 7.6 Hz), 7.65–7.70 (m, 2H), 7.54 (d, 1H, *J* = 9.2 Hz), 7.45 (t, 1H, *J* = 7.6 Hz), 7.31–7.35 (m, 3H), 7.23–7.28 (m, 3H), 6.74 (d, 1H, *J* = 9.2 Hz), 4.62 (s, 2H), 4.29 (q, 2H, *J* = 6.8 Hz), 3.23 (s, 3H), 2.51 (s, 3H), 1.37 (t, 3H, *J* = 6.8 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 12.7, 22.0, 37.5, 38.4, 49.1, 115.6, 119.7, 121.6, 123.0, 124.6, 124.8, 125.5, 125.7, 126.5, 128.7, 130.1, 132.1, 132.4, 136.1, 138.1, 138.2, 138.3, 142.7, 161.4, 166.6 ppm. HRMS: *m*/*z* calcd for $C_{27}H_{25}N_3O_4S$; [M^++H] 488.1638; found: 488.1641.