Tetrahedron Letters 57 (2016) 2311–2314

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Formation of 1,3-diazocine by palladium catalyzed C–H arylation

Le Tang [a,b], Jing Ren [a,c], Yuchi Ma [a,c], Xin Wang [a,c], Lin Chen [a,c], Jingkang Shen [a,c], Yue-Lei Chen [a,c,*], Bing Xiong [a,c,*]

[a] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, PR China
[b] College of Pharmacy, Nanchang University, 461 Bayi Road, Nanchang 330006, PR China
[c] University of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, PR China

ARTICLE INFO

Article history:
Received 21 March 2016
Revised 12 April 2016
Accepted 14 April 2016
Available online 25 April 2016

Keywords:
1,3-Diazocine
C–H arylation
8-Aminoimidazo[1,2-*a*]pyrazines
8-Membered ring
Groebke–Blackburn–Bienaymé reaction

ABSTRACT

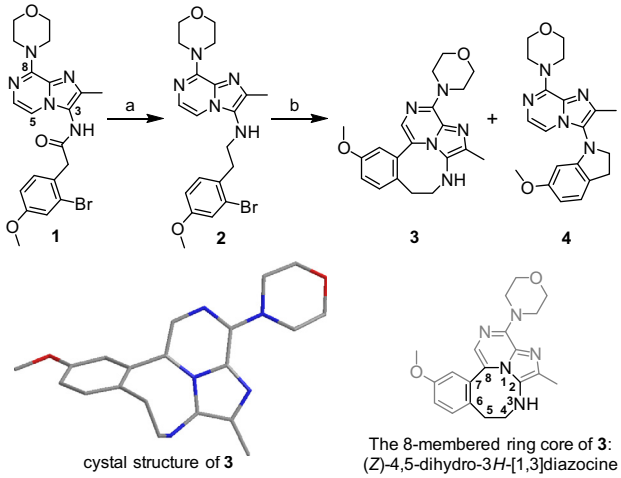
From multi-substituted 8-aminoimidazo[1,2-*a*]pyrazines, prepared via modified Groebke–Blackburn–Bienaymé reaction, a Pd-catalyzed cyclization reaction was discovered, leading to a rare (*Z*)-4,5-dihydro-3*H*-[1,3]diazocine system. Conditions of this cyclization were screened and DMF solvent was found as one of the key factors for the cyclization.

Introduction

We have previously reported the synthesis of multi-substituted 8-aminoimidazo[1,2-*a*]pyrazine by Groebke–Blackburn–Bienaymé reaction.[1] Derivatization from these 8-aminoimidazo[1,2-*a*]pyrazines was explored, and one conversion was found highly interesting. When compound **2**, prepared from compound **1** by borane reduction, was treated with $Pd(OAc)_2$ in DMF at elevated temperature, eight-membered ring product **3** was isolated,[2] along with the expected five-membered ring product **4**.[3] The structure of compound **3** was further corroborated with single crystal analysis, clearly displaying a distorted eight-membered ring system (Scheme 1).[4]

In respect of similar reactions, intermolecular C–H arylation at C-5 of imidazo[1,2-*a*]pyrazines have been reported by several groups.[5] Palladium catalysts and phosphine ligands were usually involved. In our case, phosphine ligands were found detrimental to the reaction, while DMF solvent was identified necessary for the conversion. In terms of the product structure, the central motif of compound **3** can be regarded as (*Z*)-4,5-dihydro-3*H*-[1,3]diazocine (Scheme 1), which constitutes the rare eight-membered ring heterocycles,[6] and could serve as a valuable scaffold for organic synthesis and medicinal chemistry.

Thus, we screened the cyclization condition, and prepared some useful (*Z*)-4,5-dihydro-3*H*-[1,3]diazocine derivatives with different 8-aminoimidazo[1,2-*a*]pyrazine substrates. Details of the work will be disclosed herein.

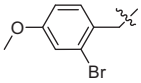
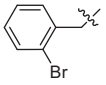
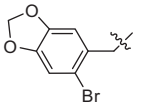
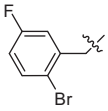
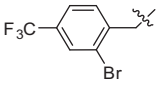
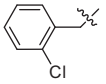
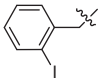
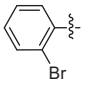
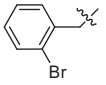
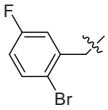
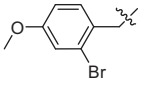
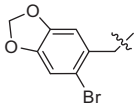
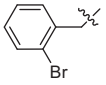


Scheme 1. Cyclization of compound **2** led to **3** containing an eight-membered ring and **4** containing a five-membered ring. Reaction conditions: (a) BH_3–THF complex, THF, 80 °C, 1–2 h; (b) $Pd(OAc)_2$, Cs_2CO_3, DMF, 70 °C, overnight. Recovered **2**: 5%; Yield of **3**: 45%; Yield of **4**: 8%.

* Corresponding authors. Tel.: +86 21 50806600x5407.
E-mail addresses: chenyuelei@gmail.com (Y.-L. Chen), bxiong@simm.ac.cn (B. Xiong).

http://dx.doi.org/10.1016/j.tetlet.2016.04.050
0040-4039/

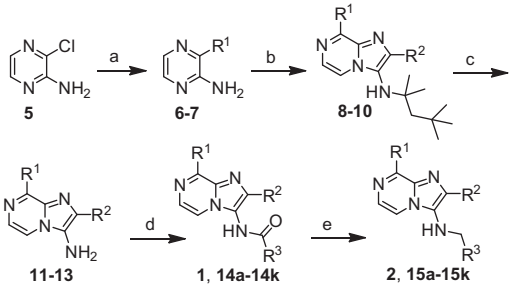
Table 1
Products and yields of the reactions described in Scheme 2

No.	R^1	Products **6–7** and yields	R^2	Products **8–10** and yields	Products **11–13** and yields	R^3	Products **1**, **14a–14k** and yields	Products **2**, **15a–15l** and yields
1		**6**, 92%	Me–	**8**, 86%	**11**, 98%		**1**, 88%	**2**, 76%
2							**14a**, 88%	**15a**, 77%
3							**14b**, 87%	**15b**, 73%
4							**14c**, 84%	**15c**, 73%
5							**14d**, 79%	**15d**, 80%
6							**14e**, 83%	**15e**, 71%
7							**14f**, 91%	**15f**, 82%
8							**14g**, 61%	**15g**, 74%
9	BnNH-	**7**, 61%	Me–	**9**, 84%	**12**, 96%		**14h**, 90%	**15h**, 83%
10							**14i**, 83%	**15i**, 87%
11							**14j**, 86%	**15j**, 85%
12				**10**, 77%	**13**, 95%		**14k**, 90%	**15k**, 74%

Results and discussion

As described in Scheme 2, to prepare 8-aminoimidazo[1,2-*a*] pyrazine substrates, pyrazine **5** was condensed with morpholine or benzylamine to produce diaminopyrazines **6** and **7**, which were subjected to a variation of Groebke–Blackburn–Bienaymé multi-component reaction (MCR) previously developed by us.[1] With two types of aldehyde components, the yields of multi-substituted 8-aminoimidazo[1,2-*a*]pyrazines **8**–**10** were generally good. Next, the alkyl protections on 3-NH_2 of compounds **8**–**10** were removed under acidic condition with excellent yields, releasing the free amines **11**–**13**, which were subjected to acylation to give compounds **1**, and **14a–14k.** At last, the amide oxygen of compounds **1**, and **14a**–**14k** were reduced by borane to afford compounds **2**, and **15a**–**15k**. Thus, in a five-step sequence, substrates for the projected cyclization study were prepared efficiently. The structures and yield details are listed in Table 1.

Meanwhile, using compound **2** as a probe, we also screened the conditions for cyclization. The results are described in Table 2. The



Scheme 2. Preparations of substrates for the cyclization study. Reaction conditions: (a) morpholine or $BnNH_2$, NMP, DIPEA,120–130 °C, 12 h; (b) $Yb(OTf)_3$, 2-isocyano-2,4,4-trimethylpentane, R^2CHO, MeOH, 65 °C, 2 h; (c) HCl/EtOAc, MeOH, 25 °C, 8 h; (d) R^3COOH, HOBt, EDCI, TEA, DCM, RT, 8 h; (e) BH_3–THF complex, THF, 80 °C, 1 h. See Table 1 and supporting information for structural and experimental details.

absence of palladium catalyst was first inspected and showed no conversion at all (Table 2, entry 1). As Snieckus et al has suggested and experimentally validated,[5b] the C–H arylation on C-5 of

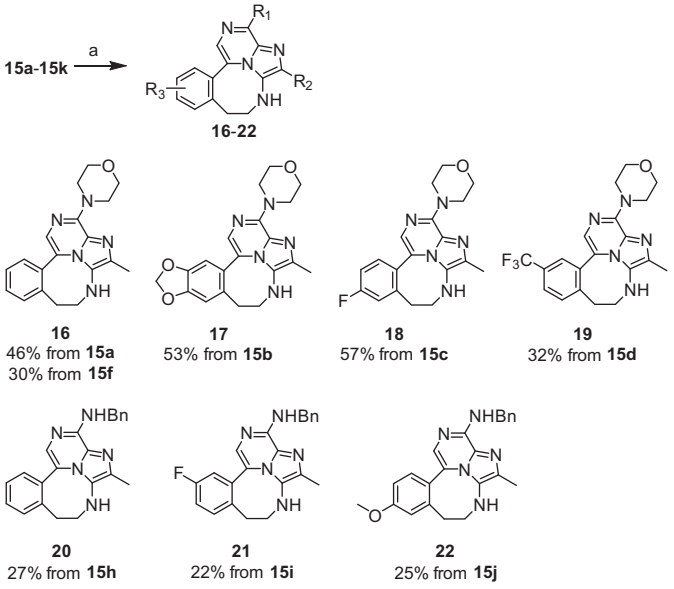
Table 2
Condition screening for the cyclization described in Scheme 1[a]

No	Catalyst	Base	Solvent	Recovered **2**	Yield of **3**	Yield of **4**
1	—	Cs_2CO_3	DMF	100%	*n.d.*[b]	*n.d.*
2[c]	$Pd(OAc)_2$	Cs_2CO_3	DMF	*n.d.*	6%	*n.d.*
3[d]	$Pd(OAc)_2$	Cs_2CO_3	DMF	41%	10%	39%
4	$PdCl_2$ $(MeCN)_2$	Cs_2CO_3	DMF	86%	*n.d.*	12%
5	$PdCl_2$(dppf)	Cs_2CO_3	DMF	*n.d.*	10%	82%
6	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	*n.d.*	14%	74%
7	10% Pd/C	Cs_2CO_3	DMF	100%	*n.d.*	*n.d.*
8	CuBr-DMS	Cs_2CO_3	DMF	100%	*n.d.*	*n.d.*
9	CuOTf-benzene	Cs_2CO_3	DMF	100%	*n.d.*	*n.d.*
10	Ni (II) acetyl-acetonate	Cs_2CO_3	DMF	100%	*n.d.*	*n.d.*
11	RhCl-$(PPh_3)_3$	Cs_2CO_3	DMF	100%	*n.d.*	*n.d.*
12	$Pd(OAc)_2$	Cs_2CO_3	toluene	100%	*n.d.*	*n.d.*
13	$Pd(OAc)_2$	Cs_2CO_3	DMAC	*n.d.*	39%	*n.d.*
14	$Pd(OAc)_2$	Cs_2CO_3	NMP	*n.d.*	36%	*n.d.*
15	$Pd(OAc)_2$	Cs_2CO_3	$HCONH_2$	96%	*n.d.*	*n.d.*
16	$Pd(OAc)_2$	Cs_2CO_3	HCO-NHMe	92%	*n.d.*	5%
17	$Pd(OAc)_2$	Cs_2CO_3	DMSO	56%	11%	*n.d.*
18	$Pd(OAc)_2$	Cs_2CO_3	HMPA	72%	7%	*n.d.*
19	$Pd(OAc)_2$	Cs_2CO_3	Sulfolane	*n.d.*	*n.d.*	*n.d.*
20[e]	$Pd(OAc)_2$	Cs_2CO_3	THF + DMF	72%	5%	16%
21[f]	$Pd(OAc)_2$	Cs_2CO_3	THF + DMF	98%	*n.d.*	*n.d.*
22[g]	$Pd(OAc)_2$	Cs_2CO_3	THF + urea	98%	*n.d.*	*n.d.*
23[h]	$Pd(OAc)_2$	Cs_2CO_3	THF + succin-imide	*n.d.*	*n.d.*	*n.d.*
24	$Pd(OAc)_2$	K_2CO_3	DMF	45%	35%	4%
25	$Pd(OAc)_2$	Na_2CO_3	DMF	75%	15%	4%

[a] Unless otherwise mentioned, 0.2 equiv of metal catalyst and 1.4 equiv of base were always reacted under nitrogen at 70 °C overnight. Yields were determined by HPLC.
[b] *n.d.*: not detected by HPLC.
[c] Reaction was performed with dry air balloon.
[d] Reaction was performed at 110 °C.
[e] With 3 equiv of DMF.
[f] With 200 equiv of DMF.
[g] With 3 equiv of urea.
[h] With 3 equiv of succinimide.

imidazo[1,2-*a*]pyrazines proceeds through Heck-type mechanism, but not C–H oxidative mechanism. Thus, we ran one control experiment with a dry air balloon, and found that the cyclization yield was significantly reduced, most probabaly due to the presence of oxygen (Table 2, entry 2). The reaction temperature was next examined, and elevated temperature decreased the yield of compound **3** (Table 2, entry 3). Therefore the reaction temperature was kept at 70 °C and palladium catalysts with different ligands were screened. It was found that no other tested palladium catalysts could compete with $Pd(OAc)_2$ in producing the 8-membered ring **3**, as other palladium catalysts promoted the formation of amination product **4** (Table 2, entries 4–7). Metal catalysts other than palladium salts, including copper, nickel, and rhodium salts, were also tested and gave no conversion to either **3** or **4** (Table 2, entries 8–11). Different reaction solvents were investigated, too (Table 2, entries 12–19). Not surprisingly, polar solvents favored the consumption of starting material **2**. Furthermore, for the 8-membered ring cyclization, certain amide solvents, including DMAc and NMP performed better than sulfoxide or phosphoramide solvents such as DMSO, sulfolane, or HMPA. To find if the amide structure supported the cyclization, stoichiometric amounts of DMF, urea, and succinimide were tested in THF solvent, and it was found that only a large excess of DMF could still enable the conversion (Table 2, entries 20–23). In addition, other alkaline bases, including Na_2CO_3 and K_2CO_3 were examined and found less efficient than Cs_2CO_3 (Table 2, entries 24 and 25). Eventually, the original cyclization condition described in Scheme 1 was found the best one so far.

Due to the important role of DMF in this cyclization, it might be proposed that it formed a catalytic intermediate with Pd.[7] Since large excess of DMF was required, and typical Pd ligands inhibited the cyclization, the contact between DMF and Pd should be weak.



Scheme 3. Cyclization reactions of compounds **15a–15k**. Reaction conditions: (a) $Pd(OAc)_2$, Cs_2CO_3, DMF, 70 °C, overnight.

The cyclization condition in Scheme 1 was then applied on substrates **15a–15k** (Scheme 3). Compounds **15a–15d** with bromobenzene side chains gave diazocine products **16–19** with 22–57% yields. The iodo-derivative **15f** did not show better cyclization yield, and the chloro-analogue **15e** failed to give cyclization. Compound **15g** with a shorter linker between imidazole ring and phenyl ring did not cyclize to a 7-membered ring, and the starting

material could be recovered, indicating the intramolecular cyclization has a unique geometry demand. Compounds **15h**–**15j** with benzylamine substitution instead of morpholin gave cyclization products **21**–**22** with low yields, indicating the C–H arylation can be sensitive to the electron density on the pyrazine ring. The last substrate **15k** with a piperonyl substitution on the imidazole ring failed to give the cyclization product. Additionally, amide **1** could not react under the same condition. Both cases again revealed the sterical requirement of the C–H arylation.

Conclusion

In summary, some new multi-substituted 8-aminoimidazo [1,2-*a*]pyrazine substrates were efficiently prepared in a 5-step procedure, including a modified Groebke–Blackburn–Bienaymé reaction. Starting from these substrates, a Pd-catalyzed cyclization reaction was discovered, leading to the formation of rare (*Z*)-4,5-dihydro-3*H*-[1,3]diazocine system, which could be useful for further study in the fields of organic chemistry and medicinal chemistry. Also, conditions of this cyclization were screened and DMF solvent was found one of the key factors for the conversion. Much information could be derived from the condition screening and could be used for further study of mechanism related to this unusual cyclization reaction.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81273368) and the National Science & Technology Major Project – Key New Drug Creation and Manufacturing Program – of China (Grant No. 2014ZX09507-002).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.050.

References and notes

1. Ren, J.; Yang, M.; Liu, H.; Cao, D.; Chen, D.; Li, J.; Tang, L.; He, J.; Chen, Y.-L.; Geng, M.; Xiong, B.; Shen, J. *Org. Biomol. Chem.* **2015**, *13*, 1531–1535.
2. See supporting information for details.
3. This is an example of intramolecular Buchwald–Hartwig amination. For several reviews of this amination: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544; (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.
4. CCDC 1446772 contains the supplementary crystallographic data for compound **3**. These data can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.)+44(1223)336–033, e-mail: deposit@ccdc.cam.ac.uk]. See supporting information for details.
5. (a) Johnson, B. M.; Huestis, M. P. *Eur. J. Org. Chem.* **2014**, *2014*, 1589–1593; (b) Wang, J.-X.; McCubbin, J. A.; Jin, M.; Laufer, R. S.; Mao, Y.; Crew, A. P.; Mulvihill, M. J.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2923–2926.
6. Except for 1,5-diazocines, other diazocines are scarce in literature. For some recent works: (a) Tellkamp, T.; Shen, J.; Okamoto, Y.; Herges, R. *Eur. J. Org. Chem.* **2014**, *2014*, 5456–5461; (b) Maggio, B.; Raffa, D.; Raimondi, M. V.; Cascioferro, S.; Plescia, S.; Sabatino, M. A.; Bombieri, G.; Meneghetti, F.; Daidone, G. *ARKIVOC* **2008**, 130–143; For reviews: (c) Rúnarsson, Ö. V.; Artacho, J.; Wärnmark, K. *Eur. J. Org. Chem.* **2012**, *2012*, 7015–7041; (d) Perlmutter, H. D. Adv. Heterocycl. Chem. In In Alan, R. K., Ed.; Academic Press, 1989; Vol. 45, pp 185–229; (e) Perlmutter, H. D.; Katritzky, A. R. Adv. Heterocycl. Chem. In In Alan, R. K., Ed.; Academic Press, 1989; Vol. 46, pp 1–72; (f) Perlllmutter, H. D. Adv. Heterocycl. Chem. In In Alan, R. K., Ed.; Academic Press, 1990; Vol. 50, pp 1–83.
7. For some examples of amide–palladium complex: (a) Liu, H.; Li, X.; Liu, F.; Tan, Y.; Jiang, Y. *J. Organomet. Chem.* **2015**, *794*, 27–32; (b) Liu, H. Y.; Wang, K.; Fu, H. Y.; Yuan, M. L.; Chen, H.; Li, R. X. *Chinese. Chem. Lett.* **2011**, *22*, 738–740; (c) Mulqi, M. d. W.; Stephens, F. S.; Vagg, R. S. *Inorg. Chim. Acta* **1982**, *63*, 197–207; (d) Srinivas, P.; Likhar, P. R.; Maheswaran, H.; Sridhar, B.; Ravikumar, K.; Kantam, M. L. *Chem.-Eur. J.* **2009**, *15*, 1578–1581.