Tetrahedron Letters 51 (2010) 1739–1741

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Intramolecular Diels–Alder synthesis of 7-aza-α-carboline compounds

Michael B. Wallace *, Nicholas Scorah, Phong H. Vu, Jason W. Brown, Jeffrey A. Stafford, Qing Dong

Department of Medicinal Chemistry, Takeda San Diego, 10410 Science Center Drive, San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 5 January 2010
Revised 22 January 2010
Accepted 25 January 2010
Available online 1 February 2010

ABSTRACT

An efficient, versatile, and scalable route for the synthesis of 7-aza-α-carboline compounds is described. The tricyclic system has been prepared from modified pyrazinones using a key intramolecular [4+2] Diels–Alder transformation.

α-Carboline compounds have shown potential in numerous drug discovery applications, such as antiviral agents and inhibitors for oncology targets and metabolic diseases.[1] In the course of our recent medicinal chemistry efforts, we designed and pursued a novel series of compounds built upon a 7-aza-α-carboline scaffold (Fig. 1). For SAR purposes, we required a synthetic scheme that would be amenable to substitution at the 3-, 5-, and 8-positions of the core. Syntheses of modified α-carboline systems have been widely reported.[2] However, convenient approaches to the synthesis of a functionalized 7-aza-α-carboline core are severely limited.[3]

The intramolecular Diels–Alder reaction has proven to be a powerful transformation utilized in the synthesis of complex heterocyclic systems.[4] Hoornaert and co-workers described an elegant route to the synthesis of α- and β-carbolines from pyrazinones via a key intramolecular Diels–Alder reaction step (Fig. 2).[5] We sought to adopt a modification of this methodology in order to access the 7-aza-α-carboline core.

The synthesis of the functionalized 7-aza-α-carboline scaffold is outlined in Scheme 1. The known dichloropyrazinone compounds **1a** and **1b** were synthesized from the reaction of an *N*-benzylic cyanomethylamine with oxalyl chloride.[6] Selective 2-chloro displacement with the substituted 2-aminopyridine **2a** and **2b** under basic conditions produced compounds **3a–c** in moderate yields. The subsequent reaction with ethynyltrimethylsilane using Sonogashira coupling conditions provided the acetylene-containing pyrazinone intermediates **4a–c**.

The Diels–Alder reaction of compounds **4a–c** by thermolysis in toluene proceeded with the loss of ClCN (Fig. 3) to give compounds **5a–c** in high yields. The TMS group of **5a–c** was converted to an iodo group using Lewis acid catalyzed iodination conditions[7] to yield compounds **6a–c**. The Suzuki coupling reaction of **6a–c** with 3-(ethylsulfonyl)-phenylboronic acid afforded compounds **7a–c**.

Deprotection of the benzyl analogue **7a** proved to be an inefficient process. Acylation of the indole nitrogen with acetic anhydride followed by hydrogenation in the presence of palladium hydroxide gave the benzyl-deprotected product **8a** in 24% yield, along with starting material and a complex mixture of over-reduced by-products. The electron-withdrawing effect provided by the indole acyl group seemed to be necessary for successful debenzylation. In addition, acylation facilitated the reaction by improving the solubility of intermediate **7a**. De-acylation occurred slowly during the hydrogenation process. Chlorination of the pyridone **8a** with $POCl_3$ gave compound **9a** in high yield.

The use of a *p*-methoxybenzyl-(PMB)-protecting group provided a more facile and high-yielding conversion of **7** into **9**. The PMB deprotection and pyridone chlorination was accomplished in a single high-yielding step with $POCl_3$ in the presence of tetramethylammonium chloride. With the successful synthesis of our target 8-chloro compounds (**9a** and **9c**), we had versatile intermediates which could be used for 8-position SAR development via displacement reactions and palladium-coupling chemistry.

The inverse demand Diels–Alder reaction required a sufficiently electron-rich dienophile for compatibility with the electron defi-

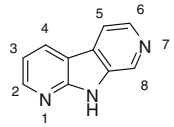


Figure 1. 7-Aza-α-carboline core.

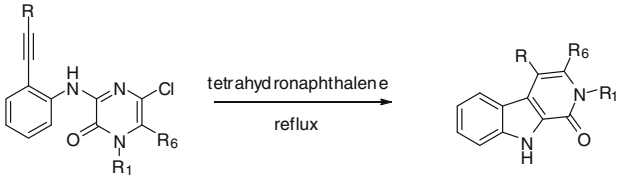
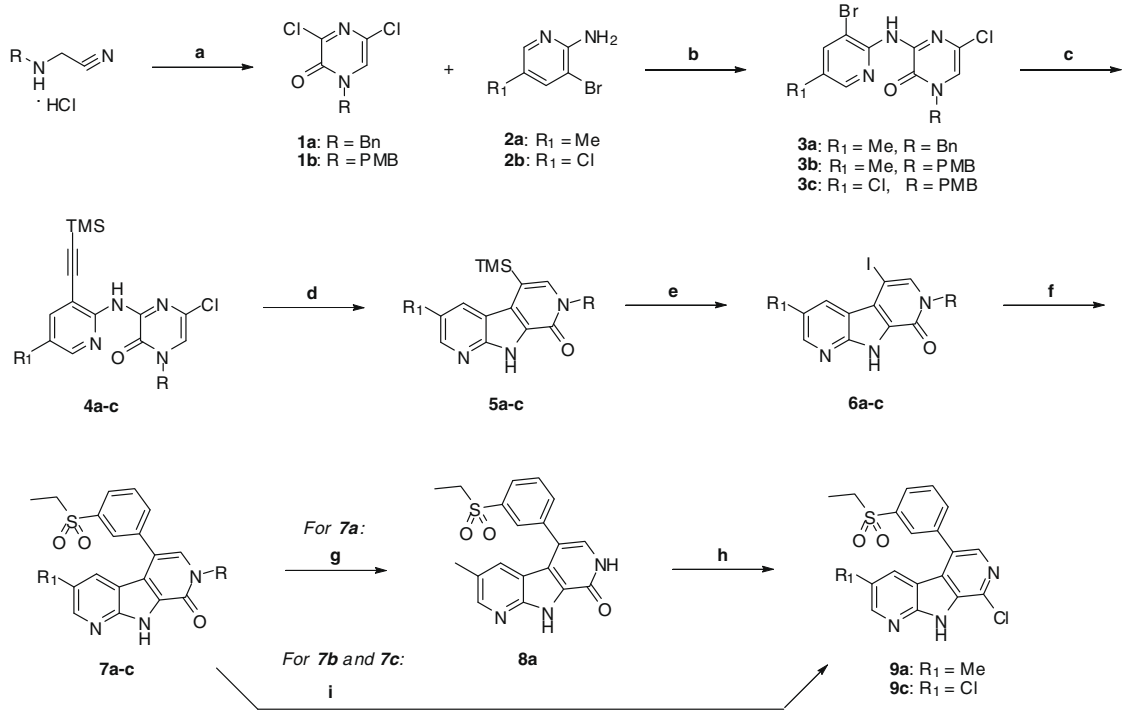


Figure 2. Key β-carboline synthesis step.

* Corresponding author. Tel.: +1 858 731 3598; fax: +1 858 550 0526.
E-mail address: michael.wallace@takedasd.com (M.B. Wallace).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.01.095



Scheme 1. Synthesis of the functionalized 7-aza-α-carboline compounds **9a** and **9c**. Reagents, conditions, and yields: (a) $(COCl)_2$, $Et_3N{\cdot}HCl$, chlorobenzene (85%); (b) NaH, THF (40–72%); (c) TMS–acetylene, $(Ph_3P)_2PdCl_2$, Et_3N, Ph_3P, CuI, THF (81–96%); (d) toluene, 110 °C, 4 days (82–89%); (e) I_2, $AgBF_4$, dichloromethane (>85%); (f) 3-$EtSO_2$Ph-$B(OH)_2$, $(Ph_3P)_4Pd$, aq K_2CO_3, dioxane (68–85%); (g) 1—Ac_2O, 2—H_2, $Pd(OH)_2$, HOAc (24%); (h) $POCl_3$ (92%); (i) $POCl_3$, $Me_4N^+Cl^-$ (79–85%).

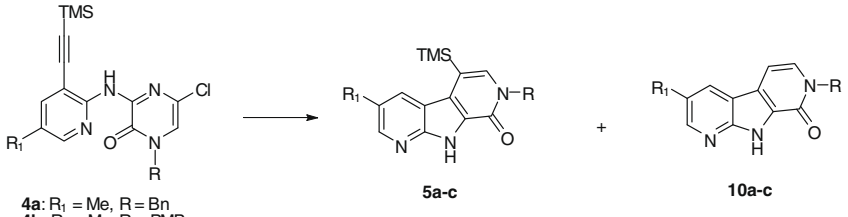
cient diene in order for the reaction to occur. When the TMS group of **4a** was replaced with an electron deficient 3-(ethylsulfonyl)-phenyl group, the Diels–Alder reaction failed to proceed.

The conditions for the Diels–Alder reaction were optimized as the scale of the reaction was increased from milligram to multi-gram quantities (Table 1). Initially, the reactions were carried out by heating the mixture for two hours in tetrahydronaphthalene at 200 °C. Yields were improved by running the reaction at lower reaction temperature (110 °C), which required longer reaction times (4 days) to push the reaction to nearly complete consumption of starting material. The solvent was changed with decreasing reaction temperature in order to facilitate its removal. The use of different non-polar solvents had no noticeable effect on the reaction.[9]

The desilylation products **10a–c** were significant side-products of the Diels–Alder reactions. Lowering the reaction temperature decreased the amount of the side-product, and the addition of diisopropylethylamine (DIEA) to the reaction eliminated it completely. The DIEA prevented the possibility of acidic desilylation caused by derivatives of the cyanogen chloride leaving group (cyanic acid, hydrochloric acid). The dilute solutions (0.01 M) favorable for the intramolecular reaction soon became impractical upon scaling the reaction to multi-gram quantities. However, at 110 °C we were also able to increase the concentration (0.04) without a decrease in product yield. Both methyl and chloro group R_1 substituents were well tolerated.

We have demonstrated an efficient, scalable route for the synthesis of functionalized 7-aza-α-carboline compounds. This meth-

Table 1
Optimization of the Diels–Alder reaction conditions



Reactant	Scale (g of **4**)	Concentration (M)	Solvent	Temperature (°C)	Time (h)	% Yield **4**[a]	% Yield **5**[b]	% Yield **10**[a]
4a	0.12	0.01	Tetrahydronaphthalene	200	2	0	51	12
4a	2.0	0.02	1,2-Dichlorobenzene	160	3.5	5	42	26
4a	3.5	0.02	Bromobenzene	140	16	6	61	9
4b	11.0	0.04	Bromobenzene	140	6	40	12	42
4b	8.8	0.01	Bromobenzene	115	48	6	73	15
4b	35.2	0.04	Toluene	110	94	1	89	2
4c	5.8	0.02	Toluene, DIEA (1.5 equiv)	110	96	2	88	0

[a] Analytical HPLC ratio analysis.[8]
[b] Isolated yield.

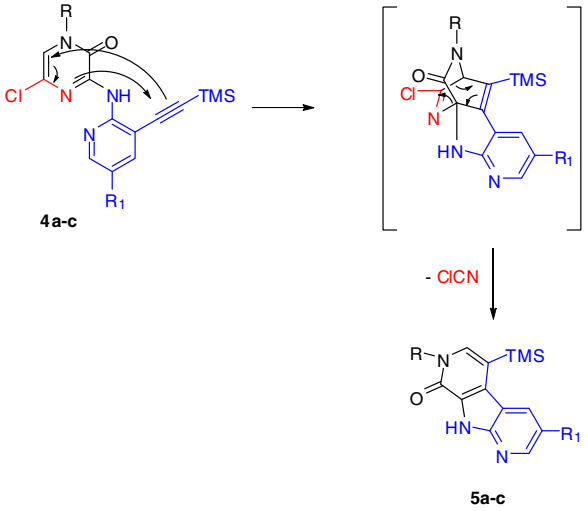


Figure 3. Proposed Diels–Alder reaction mechanism.

od allows for a high degree of diversity at the 5- and 8-positions of the tricyclic core. These results provide new possibilities for utilizing the 7-aza-α-carboline system in drug discovery.

Supplementary data

Supplementary data (chemistry experimental procedures and compound characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.095.

References and notes

1. (a) Blackburn, T. P.; Bolton, D.; Forbes, I. T.; Johnson, C. N.; Marin, R. T.; Thomas, D. R.; Thompson, M.; Upton, N. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 279; (b) Sennbenn, P.; Mantoulidis, A.; Treu, M.; Tontsch-Grunt, U.; Spevak, W.; McConnel, D.; Schoop, A.; Brueckner, R.; Jacobi, A.; Guertler, U.; Schnapp, G.; Klein, C.; Himmelsbach, F.; Pautsch, A.; Betzmeier, B.; Herfurth, L.; Mack, J.; Wiedenmayer, D.; Bader, G.; Reiser, U. U.S. Patent Appl. US 07/0004684.; (c) Kubota, H.; Miura, M.; Sasuga, D.; Moritani, H. Eur. Patent Appl. EP1367058.
2. For recent approaches, see: (a) Schmittel, M.; Steffen, J.-P.; Rodriguez, D.; Engelen, B.; Neumann, E.; Cinar, M. E. *J. Org. Chem.* **2008**, *73*, 3005; (b) Mehta, L. K.; Parrick, J.; Payne, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, *11*, 1261; (c) Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929; (d) Schneider, C.; Gueyrard, D.; Popowycz, F.; Joseph, B.; Goekjian, P. G. *Synlett* **2007**, *14*, 2237; (e) Malapel-Andrieu, B.; Mérour, J.-Y. *Tetrahedron* **1998**, *54*, 11095.
3. (a) Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Modi, H.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 5950; (b) Bhatti, I. A.; Busby, R. E.; Mohamed, M.; Parrick, J.; Shaw, C. J. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, *24*, 3581.
4. (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668; (b) Roush, W. R.. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 5. p 513.
5. Thari, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211.
6. (a) Vekemans, J.; Pollers-Wieërs, C.; Hoornaert, G. *J. Heterocycl. Chem.* **1983**, *20*, 919; (b) Rombouts, F. J. R.; De Borggraeve, W.; Toppet, S. M.; Compernolle, R.; Hoornaert, G. J. *Tetrahedron Lett.* **2001**, *42*, 7397.
7. Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* **1986**, *51*, 4833.
8. HPLC/MS compound purity data were acquired on an Agilent LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light-scattering detector (ELSD). Data are reported for HPLC product peak integration ratios at 254 nm.
9. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.