Efficient One-pot Synthesis of 1*H*-Pyrazolo[1,5-*b*]indazoles by a Domino Staudinger–Aza-Wittig Cyclization

Fen-Fen Zhao,[a] Yan-Mei Yan,[a] Rui Zhang,[b] Ming-Wu Ding*[a]

[a] Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, Central China Normal University, Wuhan 430079, P. R. of China

[b] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, P. R. of China
Fax +86(27)67862041; E-mail: mwding@mail.ccnu.edu.cn

Received: 25.08.2012; Accepted after revision: 20.09.2012

Abstract: 1*H*-Pyrazolo[1,5-*b*]indazoles were prepared via a domino Staudinger–aza-Wittig cyclization in one-pot fashion, starting from easily accessible azides and triphenylphosphine.

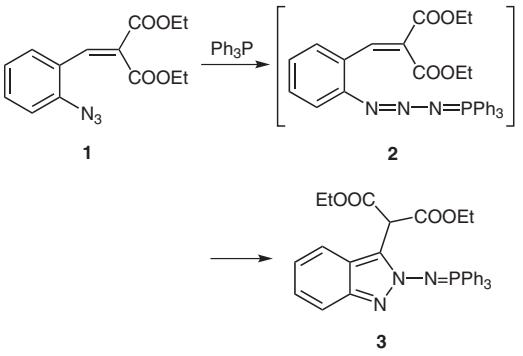
Key words: 1*H*-pyrazolo[1,5-*b*]indazole, domino reaction, aza-Wittig reaction, azide, iminophosphorane

Domino reactions have drawn great interest in modern organic synthesis and medicinal chemistry because of their ability to create structurally diverse complex molecules from simple precursors in efficient one-pot processes.[1] Compared to stepwise reactions, domino reactions have high bond-forming efficiency owning to that they can form several bonds in one sequence without isolating the reaction intermediates.

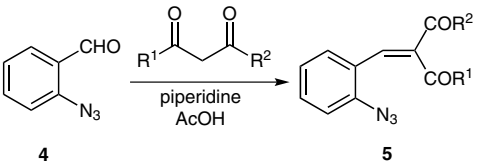
The indazole unit represents an important structural motif found in some biologically relevant compounds. Molecules containing this motif are the subject of considerable interest as potent anti-HIV,[2] antiplatelet,[3] anticancer,[4] antimicrobial,[5,6] and antifungal agents.[7,8] Much effort has been invested in the synthesis of indazoles or fused indazoles to deduce structure–activity relationships and discover new analogues with improved properties.

The aza-Wittig reaction has become a powerful synthetic tool for the preparation of acyclic and heterocyclic compounds.[9] Molina et al. have reported an effective route for the synthesis of indazoles by tandem aza-Wittig reaction (Scheme 1).[10] The intermediate indazolyl iminophosphorane **3** was directly obtained from the abnormal Staudinger reaction of the azides **1** through the phosphazide intermediate **2** in 53% yield. We envisioned that a domino Staudinger–aza-Wittig reaction would take place to give fused indazoles without isolating the iminophosphorane intermediate, if a suitable azide **1** containing a carbonyl group was used. Continuing our interest in the synthesis of N-heterocycles via the aza-Wittig reaction,[11] we wish to report herein an efficient synthesis of 1*H*-pyrazolo[1,5-*b*]indazoles by a domino Staudinger–aza-Wittig reaction in one-pot fashion.

A mixture of 2-azidobenzaldehyde (**4**) and ketones was stirred in ethanol at 0 °C for one to two hours in the presence of piperidinium acetate.[10] The condensation reaction was carried out smoothly, and the azides **5** were obtained after recrystallization in good yields (Scheme 2).[12]



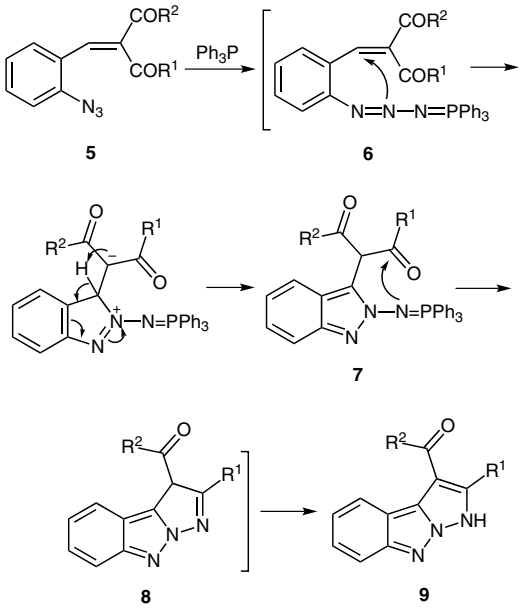
Scheme 1 Literature preparation of indazolyl iminophosphorane **3** from abnormal Staudinger reaction



Scheme 2 Synthesis of the azides **5**

When azides **5** were treated with triphenylphosphine in toluene at 0 °C for two hours, and then at refluxing temperature for two to eight hours, the previously seldom reported 1*H*-pyrazolo[1,5-*b*]indazoles **9** were isolated directly in good yields (78–90%, Scheme 3, Table 1).[13] The domino formation of 1*H*-pyrazolo[1,5-*b*]indazoles **9** can be viewed as an initial abnormal Staudinger reaction between the azide **5** and triphenylphosphine to create the phosphazide intermediate **6**, which cyclizes to give iminophosphorane **7**, probably via nucleophilic attack of the central nitrogen atom of the phosphazide moiety on the β-carbon atom of the α,β-unsaturated ketones and subsequent transformation. Further intramolecular aza-Wittig reaction of **7** produces cyclized compound **8**, in which a 1,3-H shift takes place to give the 1*H*-pyrazolo[1,5-*b*]indazoles **9**. It is noteworthy that the reaction proceeds under mild conditions to give various substituted 1*H*-pyrazolo[1,5-*b*]indazoles **9**, and the overall transformation is run in a simple one-pot procedure from azides **5** in good overall yields.

SYNLETT 2012, 23, 2850–2852
Advanced online publication: 18.10.2012
DOI: 10.1055/s-0032-1317474; Art ID: ST-2012-W0713-L

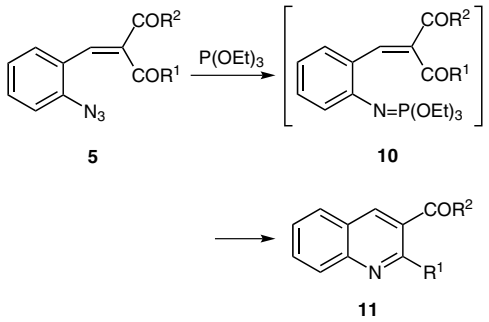


Scheme 3 Synthesis of the 1*H*-pyrazolo[1,5-*b*]indazoles **9** by domino Staudinger–aza-Wittig reaction

Table 1 Preparation of Compounds **9a–l** from Azides **5a–l**

Entry	Product **9**	R^1	R^2	Yield (%)[a]
1	**9a**	Me	OEt	90
2	**9b**	Me	Me	85
3	**9c**	Me	PhNH	82
4	**9d**	Ph	OEt	85
5	**9e**	Me	4-MeC_6H_4NH	82
6	**9f**	Me	4-ClC_6H_4NH	87
7	**9g**	Me	3-ClC_6H_4NH	81
8	**9h**	Me	2-MeC_6H_4NH	84
9	**9i**	Me	*n*-PrNH	87
10	**9j**	Me	$N(CH_2)_5$	81
11	**9k**	Ph	Ph	83
12	**9l**	4-$O_2NC_6H_4$	OEt	78

[a] Yields based on azides **5**.



Scheme 4 Literature preparation of quinolines **11** from azides **5**

It is noteworthy that Smalley et al. have reported the synthesis of quinolines **11** from the normal tandem Staudinger–aza-Wittig reaction of some azides **5** with triethyl phosphite (Scheme 4).[14] However, in our laboratory, when some azides **5** were reacted with triethyl phosphite at room temperature for two hours and then at refluxing temperature for three to four hours, only 1*H*-pyrazolo[1,5-*b*]indazoles **9** were obtained with no quinolines **11** formation.

In conclusion, we have developed an efficient one-pot synthesis of 1*H*-pyrazolo[1,5-*b*]indazoles by a domino Staudinger–aza-Wittig reaction. The mild reaction conditions and the easy availability of the starting materials make this method a valuable tool for generating 1*H*-pyrazolo[1,5-*b*]indazoles, which are of considerable interest as potential biological active compounds or pharmaceuticals.

Acknowledgment

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (No. 21032001, 21172085) and the self-determined research funds of CCNU from the colleges' basic research and operation of MOE (No. CCNU11C01002).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**.
(2) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919.
(3) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F. C.; Kuo, S.-C. *J. Med. Chem.* **2001**, *44*, 3746.
(4) Yakaiah, T.; Lingaiah, B. P. V.; Narsaiah, B.; Shireesha, B.; Kumar, B. A.; Gururaj, S.; Parthasarathy, T.; Sridhar, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3445.
(5) Yakaiah, T.; Lingaiah, B. P. V.; Narsaiah, B.; Kumar, K. P.; Murthy, U. S. N. *Eur. J. Med. Chem.* **2008**, 341.
(6) Minu, M.; Thangadurai, A.; Wakode, S. R.; Agrawal, S. S.; Narasimhan, B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2960.
(7) Park, J. S.; Yu, K. A.; Yoon, Y. S.; Han, M. R.; Kang, T. H.; Kim, S.; Kim, N. J.; Yun, H.; Suh, Y. G. *Drugs Future* **2007**, *32*, 121.
(8) Park, J. S.; Yu, K. A.; Kang, T. H.; Kim, S.; Suh, Y. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3486.
(9) (a) Naganaboina, V. K.; Chandra, K. L.; Desper, J.; Rayat, S. *Org. Lett.* **2011**, *13*, 3718. (b) Kshirsagar, U. A.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2010**, *75*, 2702. (c) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (d) Alajarin, M.; Bonillo, B.; Ortin, M.-M.; Sanchez-Andrada, P.; Vidal, A.; Orenes, R.-A. *Org. Biomol. Chem.* **2010**, *8*, 4690. (e) Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2010**, *12*, 752.
(10) Molina, P.; Conesa, C.; Alías, A.; Arques, A.; Velasco, M. D. *Tetrahedron* **1993**, *49*, 7599.

(11) (a) Xie, H.; Yuan, D.; Ding, M. W. *J. Org. Chem.* **2012**, *77*, 2954. (b) Zhong, Y.; Wang, L.; Ding, M. W. *Tetrahedron* **2011**, *67*, 3714. (c) He, P.; Nie, Y. B.; Wu, J.; Ding, M. W. *Org. Biomol. Chem.* **2011**, *9*, 1429. (d) He, P.; Wu, J.; Nie, Y. B.; Ding, M. W. *Eur. J. Org. Chem.* **2010**, 1088. (e) Li, W. J.; Liu, S.; He, P.; Ding, M. W. *Tetrahedron* **2010**, *66*, 8151. (f) Li, W. J.; Zhao, F. F.; Ding, M. W. *Synlett* **2011**, 265. (g) Xie, H.; Yu, J. B.; Ding, M. W. *Eur. J. Org. Chem.* **2011**, 6933. (h) Wu, J.; Liu, J. C.; Wang, L.; Ding, M. W. *Synlett* **2011**, 2880. (i) Nie, Y. B.; Wang, L.; Ding, M. W. *J. Org. Chem.* **2012**, *77*, 696.

(12) **General Procedure for the Preparation of Azides 5**
To a mixture of piperidine (0.85 g, 10 mmol) and AcOH (0.6 g, 10 mmol) in EtOH (10 mL) at 0 °C was added 2-azidobenzaldehyde (1.32 g, 10 mmol) and ketone (10 mmol). After stirring for 1–2 h, the solvent was evaporated under vacuum, and the residue was recrystallized to give the azide **5**.
Compound **5a**: light yellow solid (yield 89%), mp 75–76 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (s, 1 H, =CH), 7.46–7.11 (m, 4 H, ArH), 4.30–4.25 (m, 2 H, OCH_2), 2.45 (s, 3 H, CH_3), 1.24–1.20 (m, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): d = 194.7, 167.1, 139.3, 136.2, 135.5, 131.6, 128.9, 124.6, 118.3, 61.5, 26.4, 13.7 ppm. MS (EI, 70 eV): *m/z* (%) = 259 (4) [M^+], 231 (12), 217 (19), 203 (27), 143 (100), 115 (58). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.01; H, 4.92; N, 16.02.

(13) **General Procedure for the Preparation of 9**
To a solution of azide **5** (2 mmol) in dry toluene (10 mL) was added dropwise a solution of Ph_3P (0.52 g, 2 mmol) in toluene (10 mL) at 0 °C. The reaction mixture was stirred for 2 h and then was refluxed for 2–8 h. The mixture was condensed, and the precipitate was collected or the residue was chromatographed (PE–Et_2O, 4:1) on a silica gel column to give 1*H*-pyrazolo[1,5-*b*]indazole derivatives **9**.
Compound **9a**: white solid (yield 90%); mp 193–194 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 12.0 (s, 1 H, NH), 8.27 (d, *J* = 7.8 Hz, 2 H, ArH), 7.54–7.32 (m, 4 H, ArH), 4.45 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.67 (s, 3 H, CH_3), 1.50 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.0, 152.7, 143.4, 135.5, 128.4, 123.0, 122.4, 116.2, 110.8, 100.2, 59.9, 14.8, 14.3 ppm. MS (EI, 70 eV): *m/z* (%) = 243 (39) [M^+], 198 (10), 144 (100). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.89; H, 5.22; N, 17.32.

(14) Luheshi, A. B. N.; Salem, S. M.; Smalley, R. K. *Tetrahedron Lett.* **1990**, *31*, 6561.

