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A new route to phenazines†

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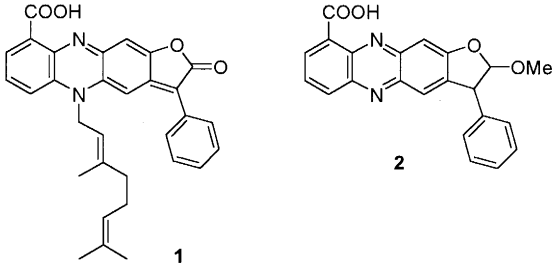
Abstract

Phenazines were prepared by the palladium(II)-catalyzed intramolecular amination of aryl bromides **8**, which were prepared with *o*-bromonitrobenzenes **3** and anilines **4** or **3** and *o*-bromoanilines **5** using palladium(II)-catalyzed aniline arylation.

Keywords: phenazines; synthesis; Pd(II)-catalyzed cyclization.

Naturally occurring phenazines have attracted considerable attention because of their interesting biological activities.[1] One of the most promising methods for synthesizing polysubstituted phenazines developed by Holliman and co-workers[2] was the reductive cyclization of *o*-nitrodiphenylamines (Method C in Scheme 1). However, the yield was poor when competitive cyclization occurred. Recently, *N*-arylation has become more accessible owing to the advent of a new methodology developed by Hartwig and Buchwald.[3] Here, we report on the use of the new method to synthesize phenazines using sequential aniline arylation.

For the total synthesis of benthocyanin A **1**, a powerful radical scavenger from the mycelium of *Streptomyces prunicolor*,[4] we needed a method to construct phenazine **2**.



Our method is based on the regiospecific bromination of *o*-nitrodiphenylamine **6**, which is obtained from **3** and **4** by aniline arylation, to give bromide **7** (Method A), which is also obtainable from

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† This paper is dedicated to Emeritus Professor, Dr. Takashi Kubota (Osaka City University) on the occasion of his 90th birthday.

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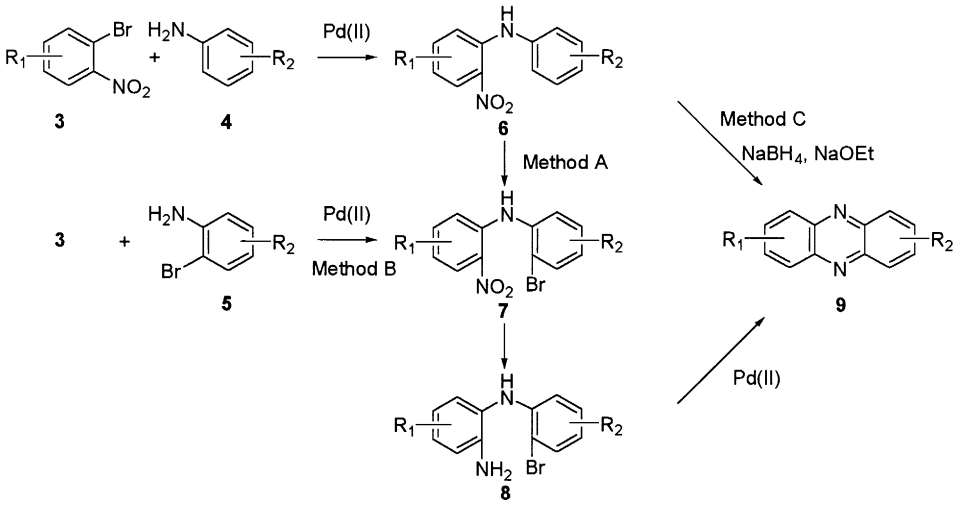
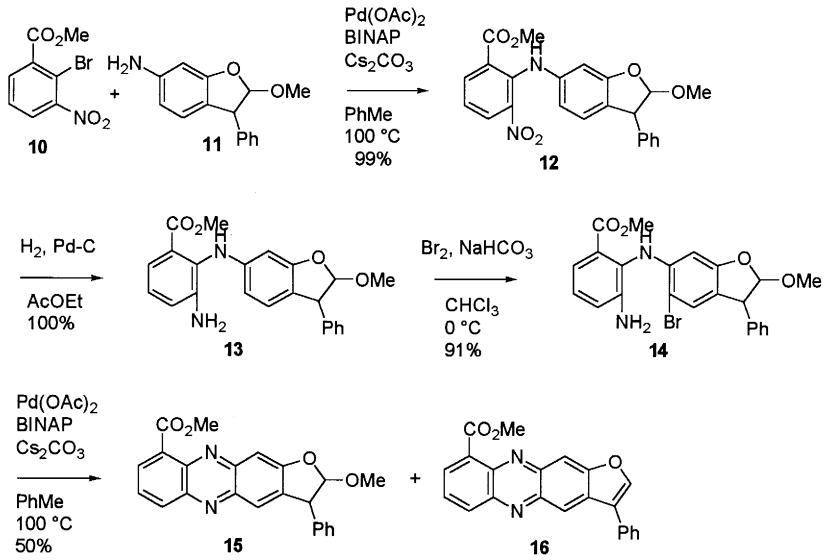


Scheme 1.

3 and **5** (Method B). Subsequent chemoselective reduction of the nitro group on **7** followed by the Hartwig–Buchwald aniline arylation affords the target phenazine **9** (Scheme 1).

Treatment of **10** and **11**[5] with palladium(II) acetate under the condition of Buchwald[6] gave the *o*-nitrodiphenylamine **12** in 99% yield. Catalytic hydrogenation of **12** in the presence of Pd–C as a catalyst gave the *N*-aryl-1,2-phenylenediamine **13** in quantitative yield. Selective bromination of **13** with bromine in the presence of sodium hydrogencarbonate at 0°C gave the *N*-(2-bromophenyl)-1,2-phenylenediamine **14** in 91% yield. This was then subjected to the cyclization again using Buchwald's condition[6] to give the desired phenazine **15** as a yellow powder together with the eliminated product **16** as orange needles (50%, **15**:**16**=3:1**)** (Scheme 2).[7]

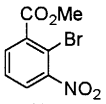
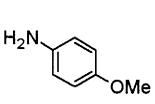
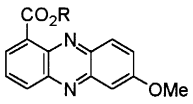
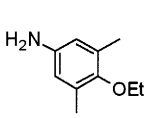
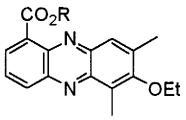
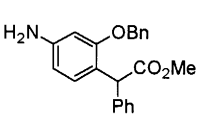
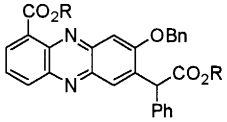
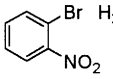
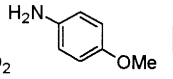
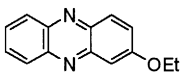
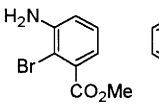
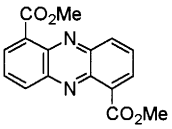
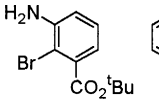
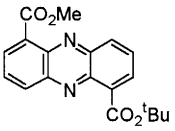
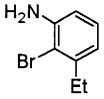
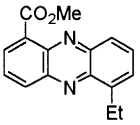


Scheme 2.

Additional examples of phenazine synthesis using this sequence of reactions in comparison with those of Holliman's are given in Table 1.[7] Our method gave yields comparable with those of Holliman's in spite of the rather longer reaction sequence. When the selectivity of the bromination was assured,

phenazines were obtained in good yields. In entry 4, there was no selectivity at the bromination step in Method A giving a complex mixture of phenazines. In Method C, 2-ethoxyphenazine was obtained in 46% yield instead of 2-methoxyphenazine. When 2-bromoanilines **5** were easily prepared, phenazines were obtained in good yields (entries 5–7).

Table 1
Synthesis of phenazines

Entry	Bromide **3**	Aniline **4**	Phenazine **9**	Total yield (%) Method A	Method B [a]	Method C
1	 **10**			65 (R = Me)		80 (R = H)
2	**10**			86 (R = Me)		88 (R = H)
3	**10**			62 (R = Me)		24 (R = H)
4				—		46
5	**10**				60	
6	**10**				80	
7	**10**				81	

a) Buchwald's condition was used in the first step, then followed similar steps as in Method A.

In summary, this aniline arylation followed by aniline arylative intramolecular cyclization offers an alternative method for the synthesis of phenazines, especially when the substrate is susceptible to a strong basic condition or when selectivity is not observed at the reductive cyclization step in Method C. Further investigations are in progress.

References

1. (a) Hosoya, Y.; Adachi, H.; Nakamura, H.; Nishimura, Y.; Naganawa, H.; Okami, Y.; Takeuchi, T. *Tetrahedron Lett*. **1996**, *37*, 9227–9228. (b) Imamura, N.; Nishijima, M.; Takadera, T.; Adachi, K.; Sakai, M.; Sano, H. *J. Antibiotics* **1997**, *50*, 8–12. (c) Pusecker, K.; Laatsch, H.; Helmke, E.; Weyland, H. *J. Antibiotics* **1997**, *50*, 479–483. (d) Kim, W.-G.; Ryoo, I.-J.; Yun, B.-S.; Shin-ya, K.; Seto, H.; Yoo, I.-D. *J. Antibiotics* **1997**, *50*, 715–721. (e) Kunigami, T.; Shin-ya, K.; Furihata, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiotics* **1998**, *51*, 880–882.
2. Challand, S. R.; Herbert, R. B.; Holliman, F. G. *Chem. Commun*.**1970**, 1423–1425.
3. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 9722–9723. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575–5580, and references cited therein. For reviews, see: (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2046–2067. (d) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818. (e) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860. (f) Frost, C. G.; Mendonca, P. *J. Chem. Soc. Perkin Trans. 1* **1998**, 2615–2622, and references cited therein. For recent applications for cyclization, see: (g) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451–8458. (h) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505–1510
4. Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **1991**, *32*, 943–946.
5. The acetal **11** was prepared from 1-chloro-2-methoxymethoxy-4-nitrobenzene by the following sequence of reaction: (1) nucleophilic substitution with the carbanion derived from methyl phenylacetate; (2) reduction of the nitro group; (3) dibenzylation of the amino group formed; (4) reduction of the ester to an aldehyde by DIBAL-H; (5) acid-catalyzed acetalization in methanol; and (6) deprotection of the dibenzylamino group.
6. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264–1267.
7. All new compounds were characterized fully by spectroscopy and high-resolution mass spectra.