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A Pummerer-based generation and trapping of furo[3,4-*c*]pyridines: an approach to nitrogen containing heterocyclic analogues of 1-arylnaphthalene lignans

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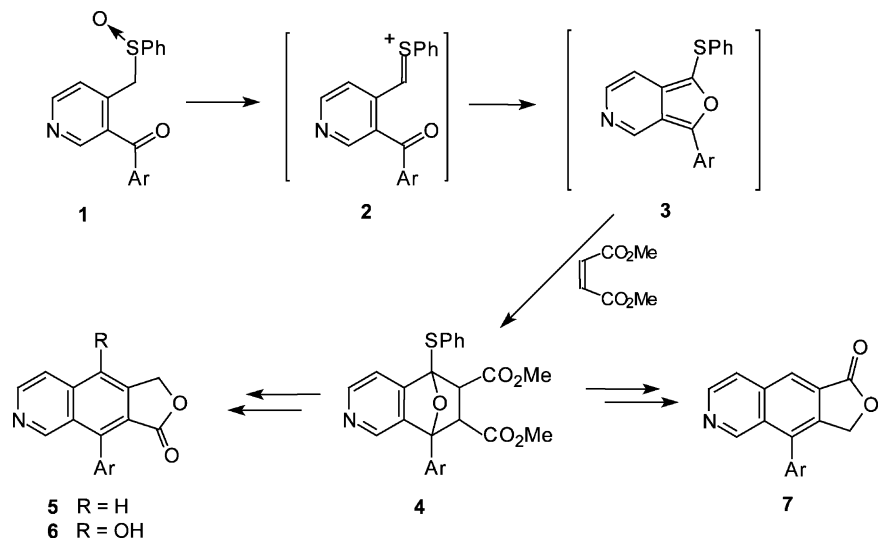
Abstract—The Pummerer reaction of *o*-benzoyl substituted pyridylmethyl sulfoxides generates α-thiocarbocations, the interception of which by the neighbouring keto functionality produces thio-substituted furo[3,4-*c*]pyridines as transient intermediates; the latter undergo [4+2] cycloaddition with an added dienophile. Base-induced ring opening of the cycloadducts followed by aromatization gives substituted isoquinolines related to heterocyclic analogues of 1-arylnaphthalene lignans.

In contrast to the phenomenal growth of the chemistry of *o*-quinoid 10-π electron isobenzofuran ring system, heteroisobenzofurans such as furo[3,4-*c*]pyridines have not been studied so well.[1–3] Recently, in a series of papers we have described the use of both stable as well as reactive furo[3,4-*c*]pyridine intermediates in the synthesis of polycyclic ring systems involving tandem[4] Hamaguchi–Ibata and Diels–Alder reactions.[5–7] In continuation of our work in this area, we now report the first Pummerer based generation[8,9] of furo[3,4-*c*]pyridines and their applications in the synthesis of substituted isoquinolines related to the nitrogen containing heterocyclic analogues of 1-arylnaphthalene lignans.[10]



Scheme 1.

Keywords: azaisobenzofuran; Pummerer rearrangement; Diels–Alder reaction; heterolignan.
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Our strategy towards arylisoquinoline lignans **5**–**7** is outlined in Scheme 1. This involves generation of α-thiocarbocation **2**[8,9] from sulfoxide **1** and its interception by a neighbouring carbonyl group to give furo[3,4-*c*]pyridine **3**; the latter should undergo a Diels–Alder reaction with an added dienophile to give **4**, which is readily convertible to heterolignans **5**–**7**.

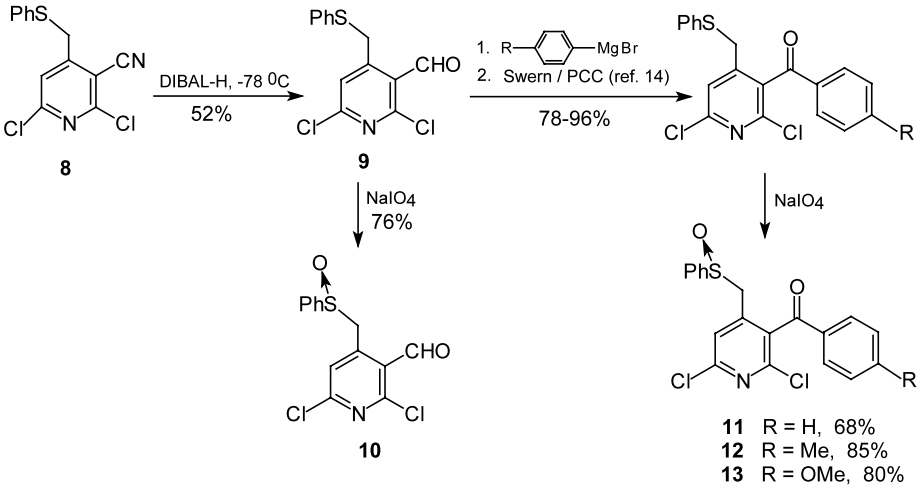
In this context, a series of pyridine containing sulfoxide precursors **10**–**13** was synthesized from the readily available nitrile **8**[11] by a standard synthetic protocol as shown in Scheme 2.[14]

To test the viability of the proposed sequential Pummerer-Diels–Alder process, we first treated simple sulfoxide **10**[15] with a suitable dienophile under standard Pummerer reaction conditions.[8,9] Thus, exposure of **10** to a mixture of acetic anhydride, dimethyl maleate and a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene for 30 min gave **14**,[16] in 44% yield, as a white crystalline solid, mp 109–111°C (Scheme 3). In this case, the [4+2] adduct (cf. **4**) underwent spontaneous ring cleavage followed by dehydration.

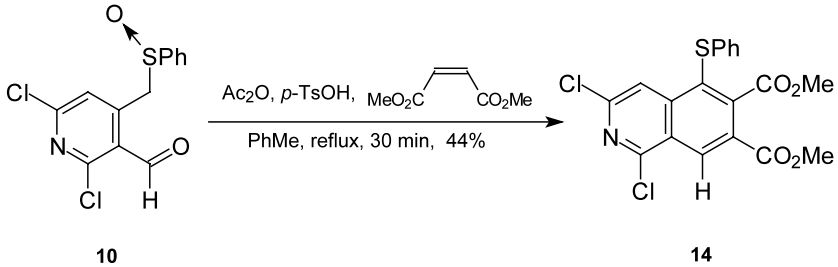
However, when keto-sulfoxide **11** was used, the sequential Pummerer-Diels–Alder reaction proceeded as expected, but here only the bridged product **15**[17] (mp 174–175°C) was obtained in 17% yield (Table 1). The stereochemistry of **15** is tentatively assigned on the basis of the Alder *endo* rule.[18] Similarly, keto-sulfoxides **12** and **13** gave **16** (mp 200–202°C) and **17**[18] (mp 164–166°C) in only 18 and 20% yield, respectively. Thus, this route turns out to be less efficient in all these cases. This prompted us to develop improved conditions for this type of sequential reaction. After considerable efforts with a variety of Pummerer promoters, we overcame this difficulty simply by replacing acetic anhydride by heptafluorobutyric anhydride. In this modified protocol (conditions B), keto-sulfoxides **11**–**13** smoothly gave bridged cycloadducts **15**–**17** with improved yields as shown in Table 1.

The oxa-bridge in the initially formed cycloadducts **15**–**17** could be readily cleaved leading to substituted isoquinolines **18**,[19] **19** and **20** using DBU in refluxing toluene (Scheme 4).[20] The synthesis of these compounds can also be conducted in one-pot by exposing keto-sulfoxides to the Pummerer conditions (conditions B) and then adding DBU to the reaction mixture.

In conclusion, we have demonstrated a Pummerer-based route for the generation of transient furo[3,4-*c*]pyridines. Further work utilizing the thio-substituted azaisobenzofuran-derived cycloadducts **15**–**17** for the synthesis of arylisoquinoline lignan analogues (cf. **5**–**7**) of potential biological interest is currently underway in this laboratory.

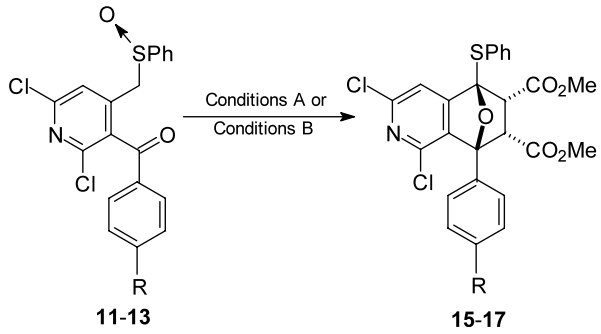


Scheme 2.



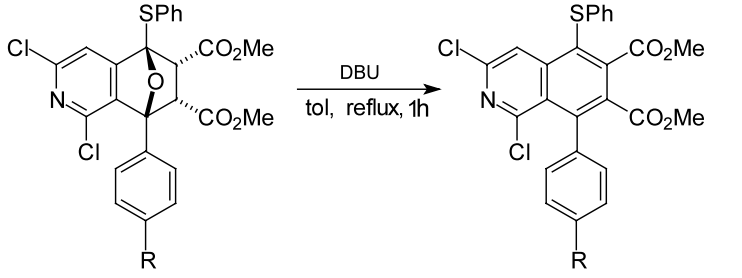
Scheme 3.

Table 1.



Substrate	R	Product	Conditions A[a] yield (%)	Conditions B[b] yield (%)
11	H	**15**	17	33
12	CH_3	**16**	18	37
13	OMe	**17**	20	40

[a] Conditions A: Ac_2O, *p*-TsOH (cat.), dimethyl maleate, PhMe, reflux, 1 h.
[b] Conditions B: $(C_4F_7CO)_2O$, *p*-TsOH (cat.), dimethyl maleate, PhMe, reflux, 1 h.



Scheme 4.

Acknowledgements

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10. For a review on heterolignans, see: Ramos, A. C.; De Clairac, R. P.-L.; Medarde, M. *Heterocycles* **1999**, *51*, 1443.
11. Compound **8** (mp 118–119°C) was prepared via base-induced condensation[12] of ethyl 4-(phenylthio)acetoacetate[13] with cyanoacetamide followed by treatment with $POCl_3$.
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14. R = H (89%, Swern); R = Me (78%, Swern); R = OMe (96%, PCC).
15. [**10**] = ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3): δ 10.27 (s, 1H), 7.50 (s, 5H), 7.05 (s, 1H), 4.75 (d, 1H, J = 11.9 Hz), 4.08 (d, 1H, J = 11.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3): δ 190.1 (d), 154.0 (s), 153.6 (s), 145.0

(s), 142.4 (s), 131.5 (d), 129.1 (d), 127.1 (d), 125.6 (s), 124.0 (d), 59.1 (t).

16. [**14**] = ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.10 (d, 1H, J = 0.9 Hz), 8.21 (d, 1H, J = 0.9 Hz), 7.30–7.07 (m, 5H); 4.01 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 167.0 (s), 164.0 (s), 152.9 (s), 147.8 (s), 144.5 (s), 142.8 (s), 134.9 (s), 131.9 (d), 129.4 (d), 128.9 (s), 128.5 (d), 127.2 (s), 127.0 (d), 125.5 (s), 118.9 (d), 53.2 (q), 53.0 (q).
17. [**15**] = ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3): δ 7.70–7.25 (m, 11H), 4.16 (d, 1H, J = 11.2 Hz), 3.61 (d, 1H, J = 11.2 Hz), 3.57 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3): 168.9 (s), 167.6 (s), 157.2 (s), 148.7 (s), 137.7 (s), 135.3 (d), 133.9 (s), 129.5 (d), 129.4 (d), 129.1 (d), 128.4 (d), 128.0 (d), 127.9 (s), 127.7 (s), 117.9 (d), 93.7 (s), 89.8 (s), 53.5 (d), 52.5 (d), 52.3 (q), 51.9 (q).
18. Support for such an assignment came from the X-ray crystal structure determination of **17**, details of which will be published elsewhere.
19. [**18**] = mp 178–179°C; ^{1}H NMR (200 MHz, $CDCl_3$:CCl_4 7:3): δ 8.37 (s, 1H), 7.48–7.35 (m, 4H), 7.32–7.15 (m, 6H), 3.88 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$:CCl_4 7:3): 166.9 (s), 166.5 (s), 151.7 (s), 146.2 (s), 142.7 (s), 141.6 (s), 141.0 (s), 137.3 (s), 135.0 (s), 133.4 (s), 129.6 (d), 129.5 (d), 128.8 (d), 128.6 (d), 128.0 (s), 127.9 (d), 127.2 (d), 124. 8 (s), 119.0 (d), 53.0 (q), 52.5 (q).
20. Initial attempts for the conversion of **15**→**18** using a variety of other reagents, e.g. MeOH/HCl, *p*-TsOH in refluxing toluene and CF_3CO_2H were unsuccessful.