Pergamon

Tetrahedron Letters 43 (2002) 4777–4780

TETRAHEDRON LETTERS

Uncatalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole to activated quinones

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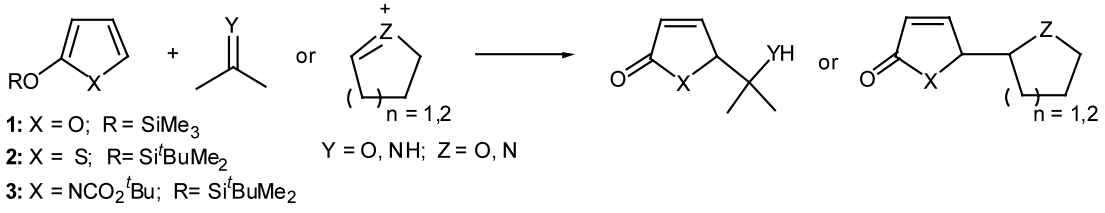
Received 2 April 2002; revised 2 May 2002; accepted 13 May 2002

Abstract—The uncatalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** to 1,4-quinones bearing an electron withdrawing group at C-2 is reported. Use of 2-methoxycarbonyl-1,4-benzoquinone **4** and 2-methoxycarbonyl-1,4-naphthoquinone **5** provided an efficient synthesis of the pyrrolidinobenzofuran adduct **9** and the corresponding pyrrolidinonaphthofuran adduct **10**, respectively, whereas use of 2-acetyl-1,4-benzoquinone **6**, 2-acetyl-1,4-naphthoquinone **7** and 2-acetyl-8-methoxy-1,4-naphthoquinone **8** formed silyloxypyrroles **11**, **12**, and **13** resulting from direct electrophilic substitution of the silyloxypyrrole by the electrophilic quinone. Addition of PPTs to the reaction of 2-acetyl-8-methoxy-1,4-naphthoquinone **8** with *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** afforded pyrrolidinonaphthofuran adduct **14** which then underwent smooth oxidative rearrangement to pyrrolidino pyranonaphthoquinone **15**, thereby providing a novel approach for the synthesis of aza-analogues of the pyranonaphthoquinone antibiotics such as kalafungin **16**.

The five-membered heterocyclic silyloxy dienes 2-trimethylsilyloxyfuran (TMSOF) **1**, 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** and *N*-(*tert*-butoxycarbonyl) - 2 - *tert* - butyldimethylsilyloxypyrrole (TBSOP) **3** provide a cohort of silyl enolate d^4 synthons that undergo vinylogous aldol-like reactions[1] with aldehydes, vinylogous imino-aldol reactions[2] (Mannich-type addition) with imines and vinylogous addition to heteroatom-stabilized carbenium ions (Scheme 1).[3] These nucleophilic modules afford highly functionalized aldol-like products that have provided synthetic platforms for further conversion to significant bioactive molecules such as the Annonaceous acetogenins,[4,5] carbasugars,[6] densely hydroxylated indolizidine alkaloids,[7] hydroxylated prolines,[8] aminosugars[9] and peptidyl *C*-glycosides.[10]

As part of our synthetic programme directed towards the synthesis of pyranonaphthoquinone antibiotics,[11] we made use of the addition of 2-trimethylsilyloxyfuran **1** to activated quinones as an efficient furofuran annulation to provide adducts that underwent subsequent oxidative rearrangement to the desired pyranonaphthoquinone skeleton (Scheme 2). Despite the extensive use of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** as a d^4 nucleophilic component in reactions with a range of electrophiles, the reaction of TBSOP **3** with quinones has not been reported. We therefore describe herein our synthetic efforts to extend our previously reported furofuran annulation of activated quinones using TMSOF **1** to an analogous pyrrolidinofuran annulation using TBSOP **3**.



Scheme 1.

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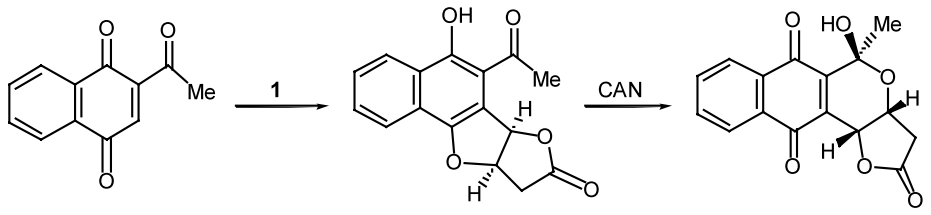
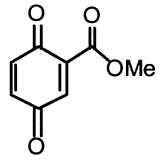
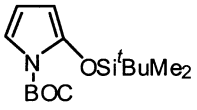
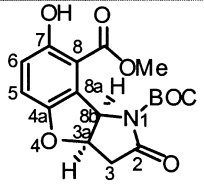
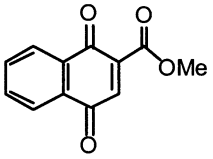
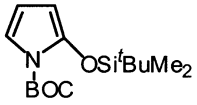
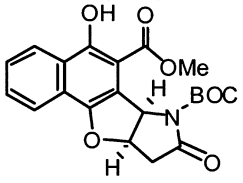
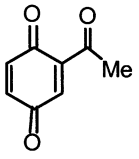
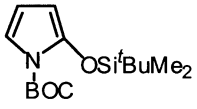
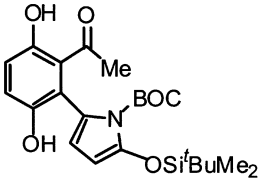
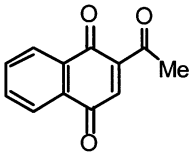
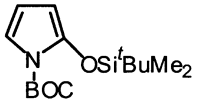
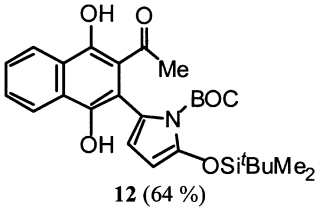
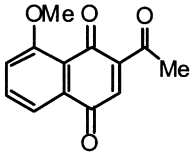
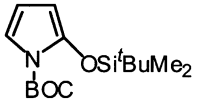
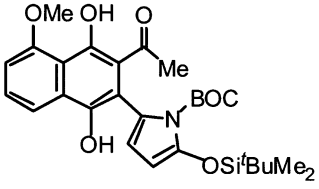
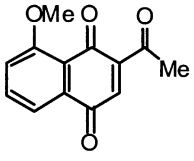
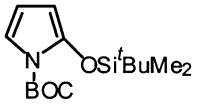
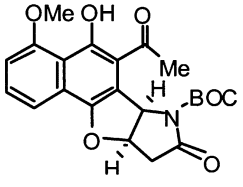
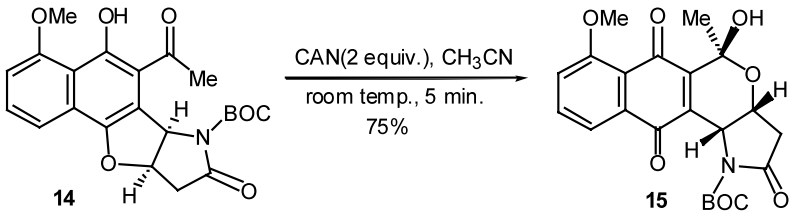


Scheme 2.

Table 1. Addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** to 2-substituted 1,4-benzoquinones and 1,4-naphthoquinones*

Quinone	Reagents	Product and Yield % [a]
		
4		**9** (36 %)
		
5		**10** (54 %)
		
6		**11** (56 %)
		
7		**12** (64 %)
		
8		**13** (38%)
	 PPTs (cat.) also added to reaction	
8		**14** (13%)

* All reactions were carried out using **3** (2.0 equiv) in acetonitrile at rt for 16 h.



Scheme 3.

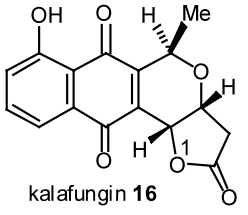
Uncatalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** (2.0 equiv.) to 2-methoxycarbonyl-1,4-benzoquinone **4** and 2-methoxycarbonyl-1,4-naphthoquinone **5** in acetonitrile at room temperature afforded pyrrolidinobenzofuran adduct **9** and pyrrolidinonaphthofuran adduct **10** in 36 and 54% isolated yield, respectively (Table 1).[12–14] The adducts **9** and **10** decomposed substantially upon purification by flash chromatography. The magnitude of the bridgehead coupling constant $J_{3a,8b}$ 5.1–5.4 Hz clearly established the *cis*-fusion of the two five-membered rings.

Analogous addition of TBSOP **3** to 2-acetyl-1,4-benzoquinone **6**, 2-acetyl-1,4-naphthoquinone **7** and 2-acetyl-8-methoxy-1,4-naphthoquinone **8** afforded hydroquinone substituted silyloxypyrroles **11**, **12** and **13** in 56, 64 and 38% isolated yields, respectively. Thus, the use of the more electron deficient 2-acetyl substituted 1,4-quinones afforded products arising from direct electrophilic aromatic substitution of the pyrrole ring. Evidence for formation of similar silyloxypyrroles in the ^{1}H NMR spectrum of the crude reaction mixtures obtained from addition of TBSOP **3** to the 2-methoxycarbonyl-substituted quinones **4** and **5** was not found.

Despite the fact that the subtle electronic differences in the quinones used afforded different products, it was hoped that silyloxypyrrole **13** could be converted to pyrrolidinonaphthofuran **14**, which would then undergo oxidative rearrangement to the desired pyrrolidino pyranonaphthoquinone **15**. This approach proved disappointing in that after considerable experimentation involving the use of many acidic-, basic- and fluoride-containing reagents, silyloxypyrrole **13** could not be induced to form pyrrolidinonaphthofuran **14**. When the initial addition of TBSOP **3** to 2-acetyl-8-methoxy-1,4-naphthoquinone **8** was carried out in acetonitrile and pyridinium *p*-toluenesulfonate (PPTs) then added directly to the reaction mixture, pyrrolidinonaphthofuran **14** was afforded albeit in 13% yield. The low yield was attributed to the inherent instability of the pyrrolidinonaphthofuran **14**.

Having encountered considerable difficulty in achieving conversion of silyloxypyrrole **13** to pyrrolidinonaphthofuran **14**, it was rewarding then to find that pyrrolidinonaphthofuran **14** underwent smooth oxidative rearrangement to the desired pyrrolidino pyranonaphthoquinone **15**[15] in good yield (Scheme 3) using ceric ammonium nitrate (CAN). The successful formation of pyrrolidino pyranonaphthoquinone **15** provides a novel approach to the basic skeleton required for the synthesis of 1-aza-analogues of the pyranonaphthoquinone family of antibiotics such as kalafungin **16**.

In summary the first study of the addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** to electron deficient quinones is reported. The adducts formed from these reactions provide novel heterocyclic ring systems that can be further elaborated to provide aza analogues of natural products, as demonstrated by the conversion of adduct **15** to the 1-aza analogue of the bioreductive alkylating agent kalafungin **16**.[16]



kalafungin **16**

Acknowledgements

Financial assistance from The University of Auckland Research Committee is gratefully acknowledged. We also thank Mr. Chris Guo and Professor Jayanta Ray for carrying out preliminary experiments using alternative quinones and silyloxypyrroles that were not fruitful.

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11. Brimble, M. A. *Pure Appl. Chem.* **2000**, *72*, 1635.
12. All new compounds gave satisfactory ^{1}H, ^{13}C NMR, IR and HRMS data.
13. A representative example of the experimental procedure—*tert-butyl (3aS*,8bS*)-8-methoxycarbonyl-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1H-[1]benzofuro[3,2-b]pyrrole-1-carboxylate* **9**. To an ice-cooled solution of 2-methoxycarbonyl-1,4-benzoquinone **4** (200 mg, 1.2 mmol) dissolved in acetonitrile (8 mL) was added a solution of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** (700 mg, 2.36 mmol) in acetonitrile (12 mL) dropwise under nitrogen. After being stirred for 2 h, the solution was warmed to room temperature then stirred for 18 h. The solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (gradient elution 9:1 to 4:6) as eluent to afford the *title compound* **9** (150 mg, 36%) as colourless crystals, mp 114–116°C (found: M^+, 349.1159, $C_{17}H_{19}NO_7$ requires 349.1161).
14. Spectroscopic data for **9**: υ_{max} (film)/cm^{-1} 3295v (OH), 2984m, 1754m (C=O), 1728m (C=O), 1683m (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, ^{t}Bu), 2.94 (2H, apparent d, *J* 5.1 Hz, H-3), 3.95 (3H, s, OMe), 5.14 (1H, t, $J_{3a,8b}$ 5.1, $J_{3a,3}$ 5.1 Hz, H-3a), 5.81 (1H, d, $J_{3a,8b}$ 5.1 Hz, H-8b), 6.93 (2H, apparent s, H-5, H-6), 9.65 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_3, C*Me*$_3$), 38.0 (CH_2, C-3), 52.1 (CH_3, OMe), 64.2 (CH, C-8b), 79.3 (CH, C-3a), 83.7 (C, *C*Me$_3$), 112.7 (C, C-8), 116.5 (CH, C-6), 119.9 (CH, C-5), 123.7 (C, C-8a), 150.2 (C, C-7), 154.0 (C, C-4a), 154.4 (C, NCO_2), 170.1 (C, C-2), 170.3 (C, CO_2Me); *m*/*z* 349 (M^+, 4%), 276 (M–O^{t}Bu, 3), 249 (M–O^{t}Bu–HCN, 70), 217 (M–O^{t}Bu–$COCH_3$, 100).
15. The stereochemistry at the hydroxyl centre in **15** was assigned by analogy to that observed for similar rearrangements of furonaphthofurans to furonaphthopyrans, see: Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 881.
16. For a review on the isolation and biological activity of pyranonaphthoquinone antibiotics, see: Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rev.* **1999**, *16*, 267.