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A Novel Phenol-Forming Reaction for Preparation of Benzene, Furan, and Thiophene Analogs of CC-1065/Duocarmycin Pharmacophores

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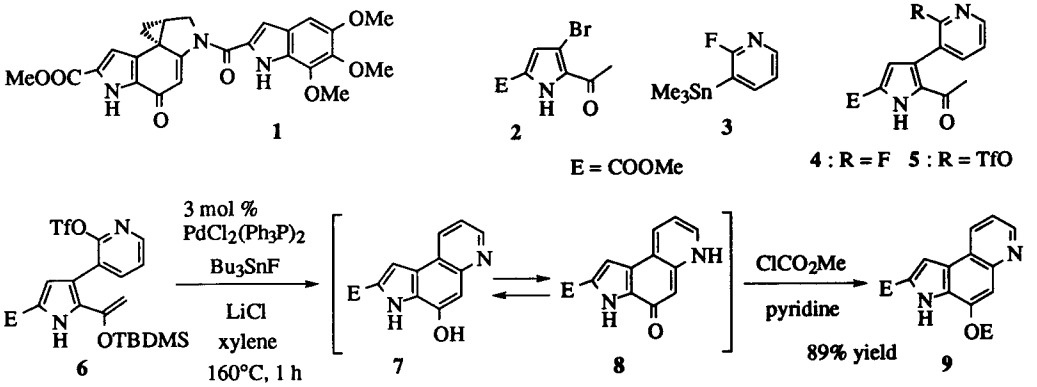
Abstract: A palladium-catalyzed intramolecular coupling reaction between methyl ketones and triflates was developed for preparation of phenol derivatives**13**, **14**, and **15** from **10**, **11**, and **12** in high yields. Potent antitumor substances **35**, **36**, and **37** were prepared from **13**, **14**, and **15**.

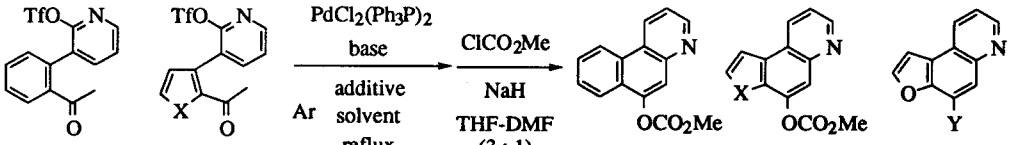
In the previous communication,[1] we reported a new synthetic pathway for duocarmycin SA (**1**),[2, 3] an extremely potent antitumor antibiotic isolated from a culture broth of *Streptomyces* species (Scheme 1).[4] This synthesis featured a ready access to the key compound **9** having a pyrroloquinolinol structure, whose pyridine part was utilized for construction of the cyclopropapyrrolidine unit in **1**. Preparation of **9** was accomplished by applying a palladium-catalyzed reaction, originally described by Kuwajima and co-workers,[5] to a silyl enol ether **6** of the triflate **5**, derived from **2** and **3** (Stille coupling to **4** and further functional modification). Reaction conditions shown below afforded a cyclized product as a mixture of valence tautomers **7** and **8**, and this was isolated in the form of methyl carbonate **9** in 89% yield calculated from **5**. However, a high yield result was only limited to this case, and when these conditions were applied to the cyclizations of benzene, furan, and thiophene derivatives **10**,[6] **11**,[6] and **12**,[6] the expected tricyclic compounds **13**, **14**, and **15** were obtained in poor to

Scheme 1



moderate yields of 24%, 27%, and 70%, respectively. In this paper, we report alternative reaction conditions applicable to these cyclizations in general.

For the first trial, the above palladium-catalyzed reaction was carried out by heating of furyl methyl ketone **11** in xylene in the presence of NaH without addition of Bu_3SnF and LiCl (Table, run 1). The desired product **14** was obtained in 9% yield, along with a variety of by-products **16**, **17**, and the pyridone derivative derived from **11**, after methoxycarbonylation. Change of the base from NaH to *t*-BuOK or K_2CO_3 completely retarded the formation of **14**, and only the above by-products were obtained in poor yields (run 2, 3). Use of Cs_2CO_3 effected the production of **14** in 26% yield, together with much decreased formations of **16** and **17** in 6% and 2% yields (run 4). Addition of Ph_3P dramatically enhanced the production of **14**, and finally, the reaction conditions shown in run 5, *i.e.*, use of 10 mol% of $PdCl_2(Ph_3P)_2$, 3 eq. of Cs_2CO_3, 0.3 eq. of Ph_3P in refluxing benzene under an Ar atmosphere, afforded the desired **14** in 90% yield without any by-product. When these reaction conditions were applied to **10** and **12**, high yield formation of **13** and **15** was also noticed as shown in runs 6 and 7. Therefore, a novel type of phenol-forming reaction has been developed using a palladium catalyst, and will be widely



10

11: X = O
12: X = S

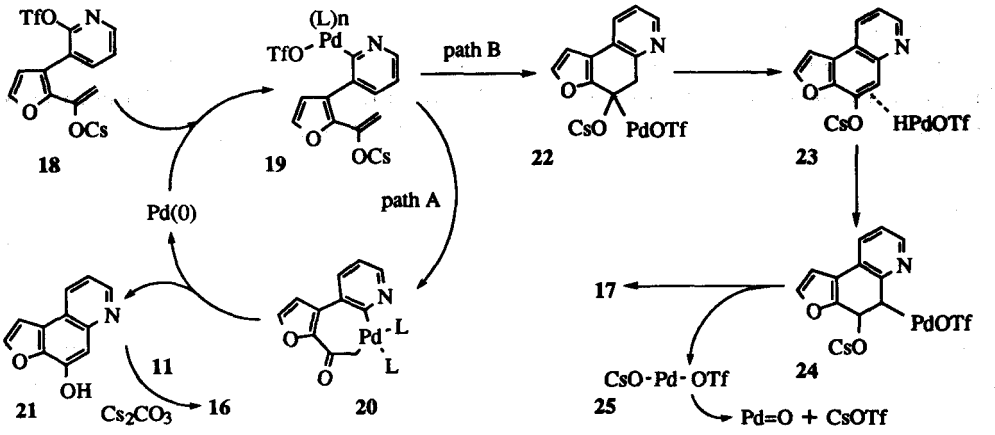
13

14: X = O
15: X = S

16: Y = OTf
17: Y = H

Run	Starting material	Pd cat. eq.	Base (eq.)	Additive (eq.)	solvent	time h	Product	By-product	Recovery
1	**11**	0.05	NaH (3)	—	xylene	16.5	**14**, 9%	**16**, 11% **17**, 6% pyridone, 13%	19%
2	**11**	0.05	*t*-BuOK (3)	—	toluene	16	**14**, 1%	**16**, 3%	5%
3	**11**	0.05	K_2CO_3 (3)	—	xylene	18	—	**16**, 18% **17**, 3% pyridone, 16%	25%
4	**11**	0.05	Cs_2CO_3 (3)	—	xylene	4.5	**14**, 26%	**16**, 6% **17**, 2%	6%
(5)	**11**	0.1	Cs_2CO_3 (3)	Ph_3P (0.3)	benzene	6	**14**, 90%	—	—
(6)	**10**	0.1	Cs_2CO_3 (3)	Ph_3P (0.3)	benzene	1.5	**13**, 91%	—	—
(7)	**12**	0.1	Cs_2CO_3 (3)	Ph_3P (0.3)	benzene	3	**15**, 86%	—	—

Scheme 2

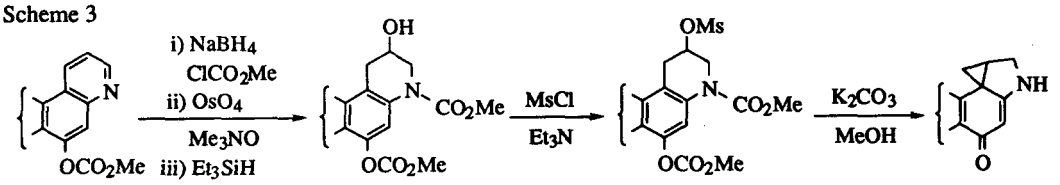


applicable to similar instances.

A precise reaction mechanism is unclear at this moment (Scheme 2). Presumably the main path A for generation of **21** starts with an intramolecular nucleophilic attack of the enolate to the palladium complex part in **19**, resulting in a cyclic palladium species **20**. This would then afford **21** on reductive elimination of Pd(0), which returns back to the reaction cycle. In some cases, **11** behaves as a sulfonating agent and **16** is partially formed from **21** in the presence of a base. For the formation of **17**, our speculation is shown in path B. Intramolecular Heck reaction in **19** will afford **22**. Then positional exchange of the palladium might take place by way of **23** to give **24**, and further elimination of **25** from **24** would afford **17**. Addition of Ph_3P may increase population of **19** bearing ligands on the palladium, and not only accelerates the path A, but also prevents the reaction course from proceeding to the path B, due to the steric hindrance in the Heck reaction.

As the requisite quinolinol derivatives **13**, **14**, and **15** became to be obtained in high yields, preparation of the key compounds **32**,[2c, 7] **33**,[2c, 8, 9] and **34**,[9] for benzene, furan, and thiophene analogs having CC-1065/duocarmycin pharmacophores, was carried out in a straightforward manner according to the previous report (Scheme 3).[1] Treatment of **13**, **14**, and **15** with $NaBH_4$ in the presence of $ClCO_2Me$ gave mixtures of 1,2- and 1,4-dihydropyridine derivatives with the CO_2Me group at the nitrogen atom. Without separation, these were dihydroxylated by oxidation with a catalytic amount of OsO_4 in the presence of Me_3NO, followed by reduction with Et_3SiH and $BF_3{\cdot}OEt_2$. The hydroxyl groups adjacent to the nitrogen and the aromatic ring were reductively eliminated, and **26**, **27**, and **28** were obtained in 68%, 67%, and 60% yields, respectively. These were mesylated,

Scheme 3



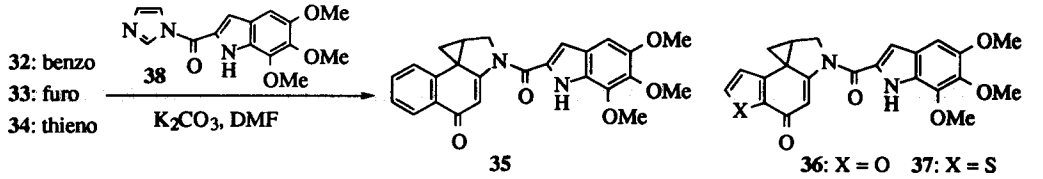
13: benzo
14: furo
15: thieno

26: benzo
27: furo
28: thieno

29: benzo
30: furo
31: thieno

32: benzo
33: furo
34: thieno

Scheme 4



and **29**, **30**, and **31**, obtained in 99%, 94%, and 95% yields, were treated with K_2CO_3 in MeOH at room temperature for 1.5 – 4 h to afford **32**, **33**, and **34** in 94%, 88%, and 93% yields. Potent antitumor compounds **35**,[2c, 10] **36**,[9] and **37**[9] were prepared in 88%, 74%, and 63% yields from **32**, **33**, and **34** by condensation with imidazolide **38** using K_2CO_3 as a reagent in DMF at room temperature. This type of reaction, *N*-acylation of the vinylogous amide, is usually carried out by treatment with NaH in DMF. In our cases, the K_2CO_3 method gave some times superior results to the conventional procedure.[11]

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6. According to the description in the ref. 1, **10**, **11**, and **12** were prepared as follows: Stille couplings between either of 2-bromoacetophenone, 2-acetyl-3-bromofuran, or 2-acetyl-3-bromothiophene and **3** afforded in 67%, 80%, and 74% yields the condensation products, which were hydrolyzed to pyridones in 97%, 90%, and 93% yields. These were triflated to **10**, **11**, and **12** in 96%, 98%, and 98% yields.
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