Pergamon

Tetrahedron Letters 39 (1998) 8051–8054

TETRAHEDRON LETTERS

Polymer-Supported Preparation of Substituted Phenols: A New Example of Simultaneous Cyclization-Cleavage Reaction on Solid Phase

Alan R. Katritzky,*[§] Sergei A. Belyakov,[§] Yunfeng Fang,[§] and John S. Kiely[‡]

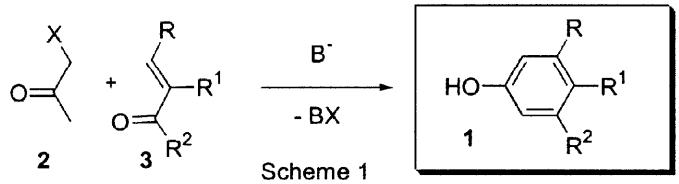
[§]Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200, USA

[‡]Trega Biosciences, Inc., 9880 Campus Point Drive, San Diego, CA 92121, USA

Received 26 May 1998; revised 5 August 1998; accepted 12 August 1998

Abstract: A series of variously substituted phenols was synthesized in high yields using the "cyclization-cleavage" approach. Base-catalyzed reactions between α,β-unsaturated ketones and polymer-bound acetonyl groups result in a tandem Michael addition/annulation reaction followed by elimination and rearrangement into phenols. Since all intermediates are on the resin until the last stage, the final reaction products contain only the desired phenols with the starting ketones as minor impurities. This efficient one-pot aromatic ring formation represents a new variant of solid phase synthesis. © 1998 Elsevier Science Ltd. All rights reserved.

Organic synthesis on solid support is now one of the most intensively studied fields of preparative organic chemistry due to the explosive development of the combinatorial approach (for recent books and reviews, *cf.* ref. 1a-d). New polymer-supported syntheses of small organic molecule libraries are now routinely reported and have become a major tool for many pharmaceutical companies. One very effective, but as yet rare method for the solid phase-supported preparation of organic cyclic molecules is the so-called "cyclization-cleavage" approach, when several synthetic transformations are carried out on polymer support, and release of the product is achieved by simultaneous cyclization and cleavage of the leaving molecule in the last reaction step. Examples of such type of reactions previously reported include preparations of lactones,[2] isoxazolines,[3] hydantoins,[4] and furans. [5a,b] The general scope of this approach is well summarized in the automated preparations of hydantoin and benzodiazepine libraries.[6] This concept for solid phase-based reactions is very attractive because of its simplicity and elegance. The number of highly efficient cyclizations familiar from solution phase organic chemistry prompted us to explore this more fully for solid phase syntheses. All previously reported transformations with this approach deal with the formation of *heteroaromatic* rings of various sizes (5-7 atoms). To the best of our knowledge, examples of similar solid-phase-supported *homoaromatic* ring system formation were previously unknown.

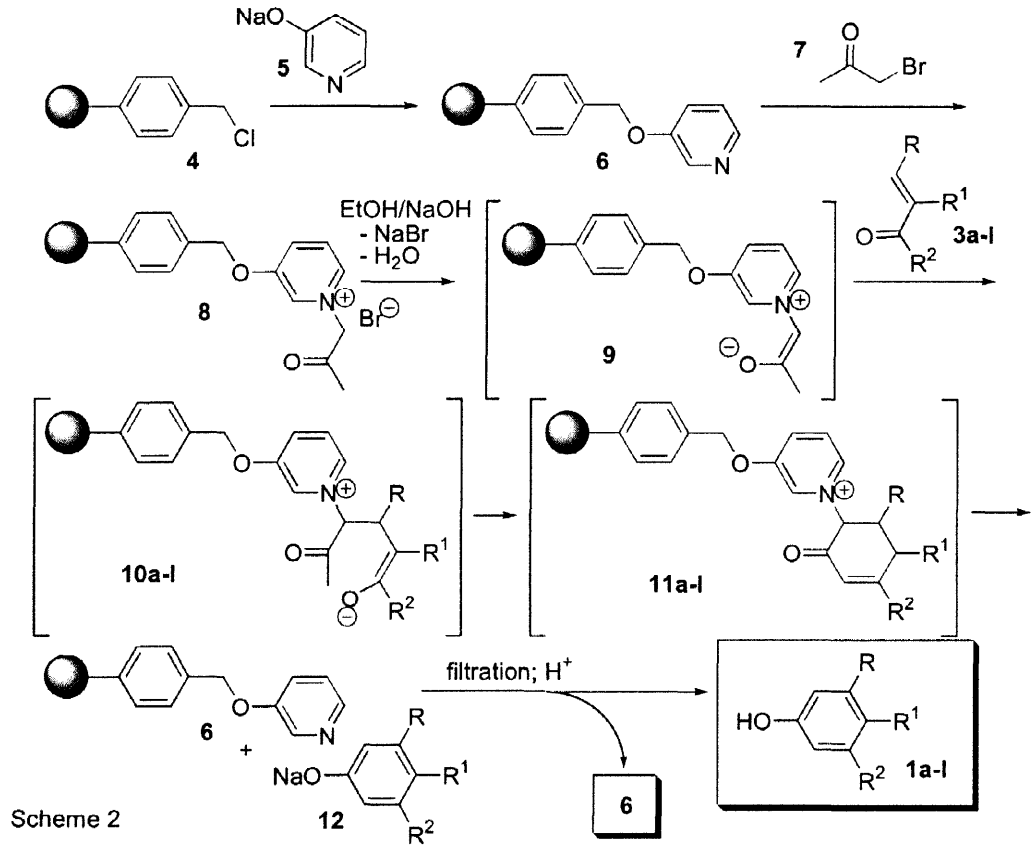


Scheme 1

Recent preparation of a phenol-derived library[7] is significant considering the well-known medicinal applications of phenol derivatives. A solution phase-based method for the preparation of 3,5-diaryl-substituted phenols was described by Eichinger *et al.*[8] We recently disclosed a more efficient and more general method for the preparation of 3,5-diaryl-substituted phenols.[9] Both reports deal with *4-unsubstituted* phenols with only

PII: S0040-4039(98)01771-7

aryl substituents at the 3- and 5-positions. The general concept for such preparation of phenols is outlined in Scheme 1. We set out to explore the solid phase-supported preparations of phenols **1** using polymer-derivatized acetonyl derivative **2**, where X represents polymer-bound linker. Ideally, this approach would allow the preparation of series of phenols substituted in the 3-, 4-, and 5-positions.



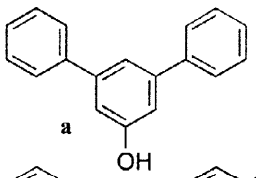
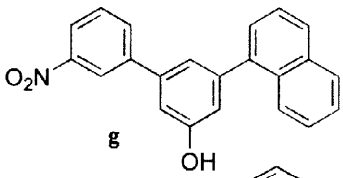
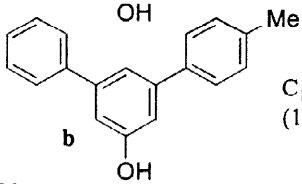
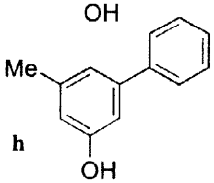
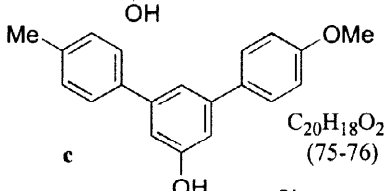
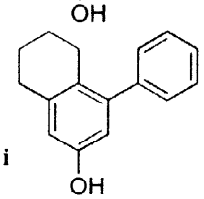
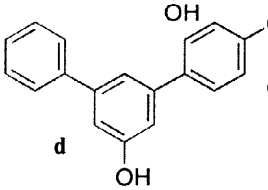
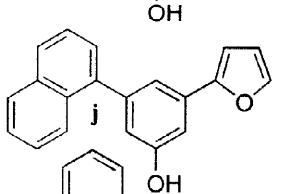
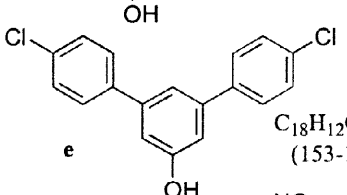
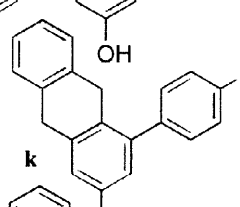
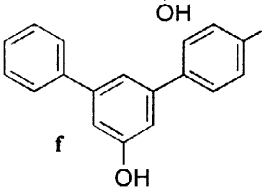
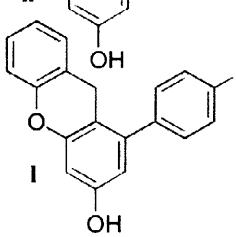
Scheme 2

We initiated our study using poly(4-vinylpyridine), a commercially available polymer with a high concentration of pyridine rings. However, the efficacy of this product was low (*ca.* 35-40% yield of 3,5-diphenylphenol **1a** after reaction with chalcone **3a**), although it did confirm the feasibility of our initial idea. The low yield may be due to steric hindrance resulting in incomplete transformation of starting chalcone into phenol **1a**. Therefore, we extended the distance between the polymer chain and the reaction site with a spacer (-Ph-CH_2O-), which allowed more flexibility for the reactant and which was easy to assemble from Merrifield resin **4** by a modification of the procedure of Frechet *et al.*[10] The loading capacity of **4** (2.91 mmol/g) was calculated based on the elemental analysis for chlorine. Reaction of resin **4** with sodium salt of 3-hydroxypyridine **5** gave polymer-bound pyridine **6**, which was successively quarternized by 2-bromoacetone to afford poly-pyridinium salt **8** (elemental analysis for bromine indicated a loading of 1.61 mmol/g).[11]

A set of model reactions allowed us to optimize the reaction time for the preparation of phenols **1a-l**. Reaction of polymer-bound pyridinium bromide **8** with chalcone **3b** was carried out for 16 h, and the amount of phenol **1b** in the reaction mixture was monitored by GC/MS. The percentage of **1b** in mixture was 81.4% after 0.5 h, 99.5% after 1 h, and then gradually diminished (93.7% after 2 h, 91.8% after 7 h, and 74.5% after 16 h), possibly, because of oxidation of **1b** during prolonged exposure to elevated temperatures under basic conditions. The molar ratio chalcone **3** : polymer **8** was also optimized experimentally and was held as 1 : 3 for the series of substituted phenol preparations. Lower ratios lead to the appearance of unreacted chalcone in the reaction mixture. Ethanol was the solvent of choice from several individual and mixed solvents tested: a

mixture of ethanol and THF (1 : 1 v/v) gave considerable starting chalcone together with other unidentified impurities, as does DMA; 2-methoxyethanol gives only 77% of phenol **1a** in the reaction mixture.[12]

Table. Solid Phase Synthesis of 3,4,5-Substituted Phenols

Phenols 1	Molecular formula (m.p.,°C)	Isolated yield, % (GC/MS purity, %)	Phenols 1	Molecular formula (m.p.,°C)	Isolated yield, % (GC/MS purity, %)
 **a**	$C_{18}H_{14}O$ (92-93)	85 (94)	 **g**	$C_{22}H_{15}NO_3$ (80-81)	81 (100)
 **b**	$C_{19}H_{16}O$ (105-106)	82 (100)	 **h**	$C_{13}H_{12}O$ (oil)	80 (94)
 **c**	$C_{20}H_{18}O_2$ (75-76)	70 (87)	 **i**	$C_{16}H_{16}O$ (oil)	52 (79)
 **d**	$C_{18}H_{13}ClO$ (113-114)	85 (100)	 **j**	$C_{20}H_{14}O_2$ (oil)	61 (99)
 **e**	$C_{18}H_{12}Cl_2O$ (153-154)	80 (95)	 **k**	$C_{21}H_{18}O$ (oil)	52 (72)
 **f**	$C_{18}H_{13}NO_3$ (165-166)	63 (97)	 **l**	$C_{20}H_{16}O_3$ (oil)	53 n/a

Apart from the desired phenols and small amounts of starting chalcones, we detected no other impurities in the reaction mixtures when ethanol was used. Results of the preparations of phenols **1a-l** are collected in the Table; they were characterized by NMR (^1H, ^{13}C), GC/MS and elemental analysis.[13] Polymers **4,6** were characterized by gel-phase ^{13}C NMR.[14] Phenols **1a-l** can be prepared by the conventional one-pot method, as was exemplified by the synthesis of 3-piperonyl-5-(4-iodophenyl)phenol (**1m**, not shown in the Table): reaction of the equimolar amounts of piperonal with 4-iodoacetophenone in EtOH/NaOH afforded the corresponding chalcone, which was converted *in situ* into **1m** (yield 62% on the starting ketone) after addition of the polymer **8** to the reaction mixture.

The reaction mechanism (Scheme 2) probably involves formation of pyridinium ylide **9** by strong base; subsequent electrophilic attack of chalcone forms intermediate pentanedione zwitterion **10**, which is cyclized into cyclohexenone derivative **11**, which in turn releases the corresponding phenolate **12** and polymer-bound pyridine **6**. Filtering off the polymer support and acidification of reaction mixture gave high purity phenols **1a-l** in good isolated yields (Table).

In summary, a new methodology has been developed for the preparation of 3,5- and 3,4,5-substituted phenols, involving tandem addition/annulation reactions of a polymer-bound *N*-acetonylpyridinium bromide and an α,β-unsaturated ketone. This method employs a simultaneous cyclization/cleavage step to release the product from the solid support. In our method, to assure that only the desired compound remains in the solution at the end of the reaction, we have exploited the solid phase nature of *N*-acetonylpyridinium component. The resin bound *N*-acetonylpyridinium bromide is used in excess to drive the reaction to completion. Thus, this method uses an easily prepared solid reagent to sweep the solution clear of the chalcone and produce the desired products in good to excellent purity. With this method we have prepared a number of novel phenols, including 3,4,5 tri-substituted and mixed aryl, alkyl examples. We believe this method is rapid, clean, and efficient and possesses high significant potential for the preparation of combinatorial libraries.

REFERENCES AND NOTES

1. (a) *Combinatorial Chemistry: Synthesis and Application*; Wilson, S. R.; Czarnik, A. W. Eds.; John Wiley and Sons, Inc.: New York, 1997; pp. 1-269; (b) *Annual Reports in Combinatorial Chemistry and Molecular Diversity*; Moos, W. H.; Pavia, M. R.; Ellington, A. D.; Kay, B. K. Eds.; Ecsom: Leiden, 1997; Vol. 1, pp. 1-354; (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449; (d) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643.
2. Moon, H.-s.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6088.
3. Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1995**, *60*, 4196.
4. Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.
5. (a) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973; (b) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139.
6. Hobbs De Witt, S.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909.
7. Meyers, H. V.; Dilley, G. J.; Durgin, T. L.; Powers, T. S.; Winssinger, N. A.; Zhu, H.; Pavia, M. R. *Mol. Diversity*, **1995**, *1*, 13.
8. Eichinger, K.; Nussbaumer, P.; Balkan, S.; Schulz, G. *Synthesis* **1987**, 1061.
9. Katritzky, A. R.; Belyakov, S. A; Henderson, S. A.; Steel, P. J. *J. Org. Chem.* **1997**, *62*, 8215.
10. Frechet, J. M. J.; de Smet, M. D.; Farrall, M. J. *J. Org. Chem.* **1979**, *44*, 1777.
11. Preparation of the resin **8**: Merrifield resin **4** (20 g) was suspended in the solution of salt **5** (22 g) in DMA (100 mL), and stirred overnight at 60-70 °C. Resin **6** thus obtained was filtered, washed extensively with THF, THF:water (1:1 v/v), THF, CH_2Cl_2, dried *in vacuo*. Resin **6** (24.7 g) was added to the solution of 2-bromoacetone (**7**) (16 g) in MeCN (200 mL) and stirred at 70-78 °C for 40 h. Work-up was similar to that described for the resin **6**.
12. All reaction conditions were similar in all trial runs: molar ratio chalcone **3** : polymer **8** : 1:3, reaction time: 1 h, temperature: 75 °C.
13. Preparation of phenols **1**: resin **8** (600 mg) and the corresponding chalcone (0.29 mmol) were added to the solution of NaOH (14 mg) in EtOH (10 mL), and the mixture was refluxed while stirring for 1 h. The resin was filtered off. Washing of the resin was performed in the same manner as above. Combined organics were acidified with HCl (10% aq) to pH 3-4, organic layer was separated, washed with saturated $NaHCO_3$, water, separated and dried over Na_2SO_4. After evaporation of the solvents, the crude product obtained was purified by column chromatography (silica, eluent - EtOAc:hexanes).
14. Resin **4**: -CH_2Cl signal position: 42 ppm; resin **6**: -CH_2O- signal position: 70 ppm. Poor swelling of polymer **8** in chloroform and even in chloroform/DMSO mixture did not allow its characterization by NMR. Bromine content in the resin **8**: 12.8%.