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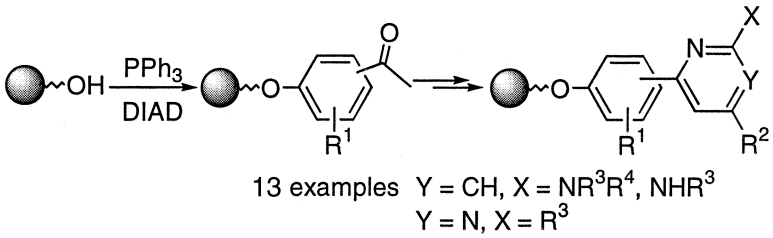

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Syntheses of 2-Alkylamino- and 2-Dialkylamino-4,6-diarylpyridines and 2,4,6-Trisubstituted Pyrimidines Using Solid-Phase-Bound Chalcones

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Several substituted 2- and 4-hydroxyacetophenones are linked to Wang resin via a modified Mitsunobu protocol. These resin-bound acetophenones are condensed with aromatic aldehydes, and the resulting chalcones **5** are used for the synthesis of 2-dialkylamino- (**9a**−**d**) and 2-alkylamino-4,6-diarylpyridines (**11a**−**f**), and 2-alkyl-4,6-diaryl- (**14a**) and 2,4,6-triarylpyrimidines (**14b,c**) in a manner suitable for combinatorial applications.

Introduction

Solid-phase organic synthesis is now extensively used for the preparation of small molecule libraries.[1a−f] Widely varied solution-phase chemistries are currently being transferred to solid phase, often involving extensive studies to develop suitable methods for solid support reactions.[1b−f] Lately, the rich chemistry of chalcones has been applied to the synthesis of pyrrolidines[2] and pyridines[3] on Wang resin and to pyrimidines, pyrazoles, and pyridines on Rink amide resin.[4] These reports have prompted us to disclose our own results in this area.

During efforts to build scaffolds for combinatorial chemistry, based on strategies developed by us in solution phase for various heterocycles, chalcones appeared to be versatile substrates. Chalcone-based libraries by the solution-phase synthesis were reported recently.[5a,b] Two main routes are available for building chalcones on solid support: (i) linking the aldehyde followed by the condensation reaction with acetophenones,[4] or (ii) linking the acetophenone followed by the condensation reaction with aldehydes.[2,3] The first approach has recently been shown to afford pure chalcones on the solid phase.[4] We believe that the low yields and loading of acetophenone onto the resin sometimes reported for the second strategy[2] could be connected with the linking procedure chosen for the acetophenone.

Results and Discussion

Significant efforts have been devoted to linking acetophenones to a solid support. Previously described methods for the preparation of acetophenone-bearing resins include (i) the acetalization of *p*-diacetylbenzene with a 1-benzyl-2,3-isopropylideneglycerol resin,[6] (ii) Pd(0) catalyzed cross-coupling of solid-phase-bound aryl iodides with 1-(ethoxyvinyl)tributyltin,[7] and (iii) nucleophilic displacement of chlorine in chloro-Wang resin by 3-acetylphenoxide anion.[2,3]

Mitsunobu reactions of Wang-type resins with phenolic substrates have proven useful for linking a wide variety of phenols bearing functional groups such as amino acids,[8] esters and cyanides,[9] aldehydes,[9−11] and chiral oxazolidinones.[12] We now show that phenols bearing enolizable groups, such as acetyl, can also be linked in this manner.

When DIAD was added to a solution of 4-hydroxyacetophenone **2a** and PPh_3 in NMM and Wang resin (Scheme 1), significant linking of byproduct (hydrazinedicarboxylate) was observed by GP ^{13}C NMR and confirmed by cleavage followed by GC−MS. However, exposure of a mixture of **2** and PPh_3 to a prolonged action of DIAD at room temperature (5 h), followed by the addition of Wang resin and running the reaction for 48 h, gave clean anchoring of **2a**−**d** to the solid support, as proved by the cleavage of pure hydroxyacetophenones **2a**−**d** from the resin (GC−MS data). The variety of hydroxyacetophenones **2a**−**d** linked cleanly onto the resin shows the generality of the method, which represents the first linkage of a phenol carrying a highly enolizable group to a Wang resin, making use of the Mitsunobu reaction. The utility of resins **3a**−**d** was demonstrated by their reactions with aromatic aldehydes **4a**−**d** which led to the synthesis of chalcones **5a**−**d** in high yields and purities (as shown by analysis of cleavage products **6a**−**d**) (Scheme 1).

Combinatorial synthesis of pyridines is still scarcely developed.[13] The three previously described combinatorial syntheses of pyridines comprise (i) an approach to 2-methyl-3-carboxypyridines by Hantzsch chemistry,[14] (ii) the preparation of 2-methyl-3-cyanopyridines via [3+3] cycloaddition from 3-aminocrotonitrile and α,β-unsaturated ketones,[4] and (iii) cyclization of 1,5-pentadiones with ammonium acetate.[3,15] Thus, a 2-aminopyridine library would fill a gap in the current solid-phase repertoire.

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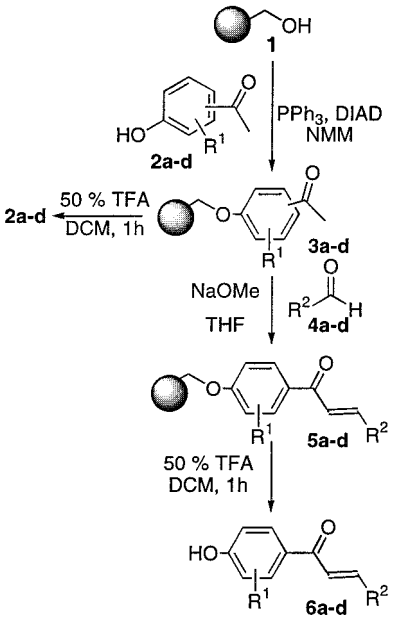
Scheme 1



2	a	b	c	d
R^1	H	3-H_3C	4-H_3CO	5-F
Purity (%)	95	98	95	90

2a,b: substituted 4-hydroxyacetophenone
2c,d: substituted 2-hydroxyacetophenone

6	a	b	c	d
R^1	H	H	H	3-H_3C
R^2	4-H_3C C_6H_4	4-H_3CO C_6H_4	4-Cl C_6H_4	C_6H_5
Purity (%)	97	95	74	90

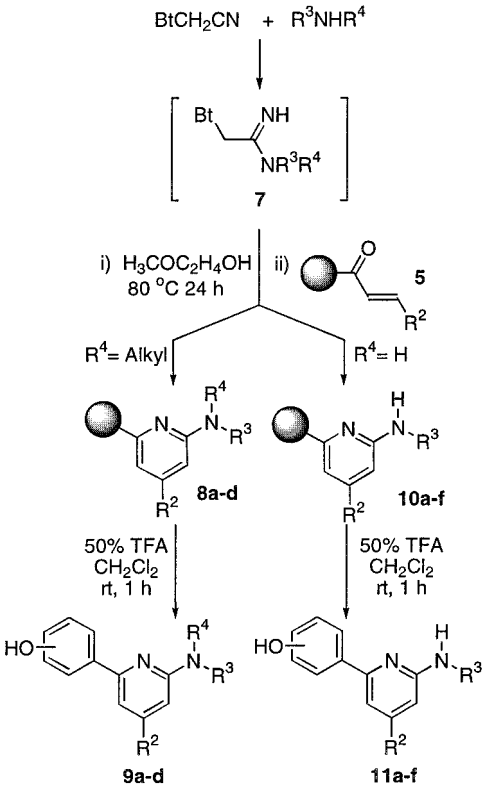
Table 1. Preparation of 2-Aminopyridines **9a**−**d** and **11a**−**f**

products	R^2	R^3	R^4	purity[c] (%)
9a[a]	4-MeC_6H_4	-$(CH_2)_4$-		95
9b[a]	4-$MeOC_6H_4$	-$(CH_2)_2$-O-$(CH_2)_2$-		76
9c[a]	4-MeC_6H_4	-CH_2(o-C_6H_4)CH_2CH_2-		75
9d[b]	Ph	-$CH_2CH_2CH_2CH(CO_2H)$-		90
11a[a]	4-MeC_6H_4	$CH_2CH{=}CH_2$	H	90
11b[a]	4-MeC_6H_4	$CH_2CH(CH_3)_2$	H	90
11c[a]	4-MeC_6H_4	*cyclo*-C_5H_9	H	90
11d[a]	4-MeC_6H_4	$CH(CH_3)C_2H_5$	H	90
11e[a]	4-MeC_6H_4	$CH_2C_6H_5$	H	80
11f[a]	Ph	$CH_2CH_2CO_2H$	H	85

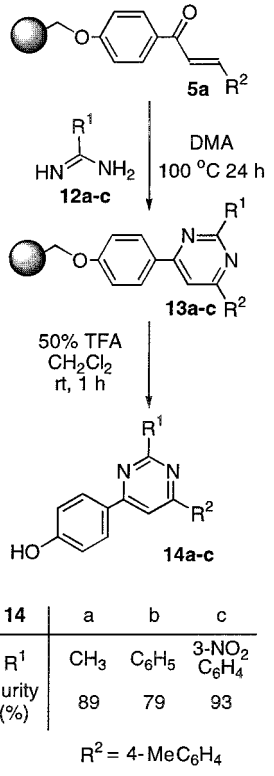
[a] Starting chalcone derived from 4-hydroxyacetophenone. [b] Starting chalcone derived from 2-hydroxyacetophenone. [c] By LC−MS.

A solution-phase synthesis of 2-(dialkylamino)pyridines based on the condensation of a chalcone, α-(benzotriazol-1-yl)acetonitrile and secondary amines was recently developed in our group.[16] This procedure has now been successfully transferred to the solid-phase synthesis of various pyridines. In a typical example, pyrrolidine was treated with a solution of α-(benzotriazol-1-yl)acetonitrile in 2-methoxyethanol at 75−80 °C for 1 day to afford an intermediate amidine **7** (Scheme 2). Without isolation, compound **7** was reacted with the chalcone-bound resin **5a** for an additional 24 h at 75−80 °C to give resin **8a**. On cleavage of **8a**, using a 50% solution of TFA in methylene chloride, 2-(pyrrolidin-1-yl)-4-(4-methylphenyl)-6-(4-hydroxyphenyl)pyridine **9a** was recovered in 90% yield with 95% purity. This protocol was successfully extended to different chalcones and various amines (Table 1), including other secondary amines (compounds **9b,c,d**), primary-alkyl primary-amines (compounds **11a,b**), secondary-alkyl primary-amines (compounds **11c,d**), a benzylic amine (compound **11e**), and also amino acids

Scheme 2



Scheme 3



14	a	b	c
R^1	CH_3	C_6H_5	3-NO_2 C_6H_4
purity (%)	89	79	93

R^2 = 4-MeC_6H_4

(compounds **9f** and **11f**). Compounds **9a**−**d** and **11a**−**f** were all obtained 75−95% pure (by LC−MS), attesting to the generality of the method. Primary amines and amino acids were condensed in high yield and purity to give an access to 2-aminopyridines bearing an additional point of diversity (compounds **11**). As shown with compounds **9b,c**, however, condensations with secondary amines were somewhat less favorable since the corresponding 2-aminopyridines were isolated typically with a purity of 75%. Moreover, aromatic amines could not be efficiently condensed with chalcone-bound resins **5**. We believe that the lower nucleophilicity of the aromatic amines retards the formation of the intermediate amidines and, therefore, of the pyridine rings.

Pyrimidines are another class of heterocycles which, alongside pyridines, constitute valuable building blocks/important pharmacophore in drug discovery. Solid-phase preparations of pyrimidines and their derivatives were recently disclosed.[4,14,17a,b] We have also studied the utility of the chalcone **5a** prepared by our new method for the synthesis of pyrimidines **13a**−**c**. Illustrative examples (Scheme 3) involve reactions of chalcone resin **5a** with acetamidines **12a**−**c** upon heating in DMA, which resulted in the isolation after cleavage of 2-substituted-4-(4-hydroxymethyl)-6-(4-methylphenyl)pyrimidines **14a**−**c**.

Conclusions

A new protocol for the preparation of resin-bound chalcones was developed through a modified Mitsunobu reaction between Wang resin and hydroxyacetophenones, followed by condensations with aryl aldehydes. Compared to the known methods, ours represents a rapid and facile solid-phase preparation of one of the most commonly used building blocks in the assembly of heterocyclic rings. Syntheses of 2-dialkylamino- and 2-alkylaminopyridines via benzotriazole mediated chemistry and pyrimidines illustrate the utility of this chemistry in solid-phase synthesis.

Experimental Section

General Methods. ^{1}H, ^{13}C, and GP ^{13}C NMR spectra were collected on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents were obtained from commercial sources and were used without purification.

General Procedure for the Preparation of Resin-Bound Acetophenones 3a−**d.** Hydroxyacetophenones (12.5 mmol) were dissolved in NMM (50 mL), followed by the addition of triphenylphosphine (3.28 g, 12.5 mmol). To the resulting solutions, DIAD (2.22 mL, 11.3 mmol) was added dropwise within 15 min. The resulting yellow solutions were reacted for 5 h at room temperature, and six tea-bags loaded with Wang resin (100 mg resin per bag, 0.79 mmol/g) were placed in the solution. The mixtures were shaken at room temperature for 48 h. Two tea-bags were taken out and subsequently washed with 2 × CH_2Cl_2, THF, THF:H_2O = 1:1, H_2O, THF:H_2O = 1:1, THF, MeOH, 2 × CH_2Cl_2 (all by 30 mL) and dried under high vacuum overnight. Cleavage was performed with 50% TFA in CH_2Cl_2 (1 h, room temperature). (**2a**: yield 85%. Purity: 95%); (**2b**: yield 90%. Purity: 98%); (**2c**: yield 85%. Purity: 95%); (**2d**: yield 90%. Purity: 90%).

General Procedure for the Preparation of Resin-Bound Chalcones 5a−**d.** Resins **3** (four tea-bags, 100 mg each, 0.34 mmol) were added to a solution of aldehydes **4a**−**d** (10 mmol) in dry THF (40 mL). A solution of sodium methoxide in methanol (25 wt %, Aldrich) was added over a 15 min period. The flask was shaken under nitrogen at room temperature for 24 h. The solution was removed, and the bags were washed with 30% aqueous AcOH, H_2O, THF, MeOH, THF, CH_2Cl_2 (all by 2 × 40 mL). The bags were dried under high vacuum over 24 h. The resins were cleaved by a 50% TFA solution in CH_2Cl_2 (1 h, room temperature).

(*E*)-1-(4-Hydroxyphenyl)-3-(4-methylphenyl)prop-2-en-1-one (6a). ^{1}H NMR δ: 2.41 (s, 3H), 6.96 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 15.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.83 (d, J = 15.6 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H). Yield: 85%. Purity: 97%.

(*E*)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (6b). ^{1}H NMR δ: 3.88 (s, 3H), 6.96 (multiplet, 4H), 7.44 (d, J = 15.5 Hz, 1H), 7.62 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 15.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 2H). Yield: 85%. Purity: 95%.

(*E*)-3-(4-Chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (6c). ^{1}H NMR δ: 6.96 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 16.4 Hz, 1H), 7.78 (d, J = 16.4 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H). Yield: 80%. Purity: 74%.

(*E*)-1-(4-Hydroxy-3-methylphenyl)-3-phenylprop-2-en-1-one (6d). Yield: 80%, purity: 90% (LC−MS).

General Procedure for the Preparation of Resin-Bound Pyridines 8a−**d and 10a**−**f.** Solutions of α-(benzotriazol-1-yl)acetonitrile (1.19 g, 7.5 mmol) and the amine of choice (7.5 mmol) in 2-methoxyethanol (30 mL) were heated at 75−80 °C for 24 h (DBU (7.5 mmol) was added for the synthesis of compounds **8d**, and **10f**). Four tea-bags of resins **5a**−**c** (100 mg of resin per bag) were added to the solutions and reacted for an additional 24 h at the same temperature. When the mixtures reached room temperature, the tea-bags were washed with DMA, THF, MeOH, THF, MeOH, CH_2Cl_2, MeOH (all by 2 × 30 mL), and the resins were dried for 1 day under high vacuum. Cleavage was performed with 50% TFA in CH_2Cl_2 (1 h, room temperature).

2-(Pyrrolidin-1-yl)-4-(4-methylphenyl)-6-(4-hydroxyphenyl)pyridine (9a). ^{1}H NMR δ: 2.03−2.09 (m, 4H), 3.57−3.63 (m, 4H), 6.43 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.30 (d, J = 7.7 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H). Yield: 90%. Purity: 94% (GC−MS), 95% (LC−MS).

General Procedure for the Preparation of Resin-Bound Pyrimidines 13a−**c.** To solutions of acetamidines **12a**−**c** (13.0 mmol) in DMA (30 mL) was added one tea-bag of resin **5a** (100 mg). The mixtures were reacted for 24 h at 75−80 °C while gently stirring the solution. When the mixture reached room temperature, the solutions were removed and the tea-bag was washed with DMA, THF, THF:H_2O (1:1), THF, CH_2Cl_2, MeOH (all by 2 × 30 mL) and then dried for 1 day under high vacuum. Cleavage was performed with 50% TFA in CH_2Cl_2 (1 h, room temperature).

2-Methyl-4-(4-hydroxyphenyl)-6-(4-methylphenyl)pyrimidine (14a). ^{1}H NMR δ: 2.49 (s, 3H), 2.96 (s, 3H), 6.85 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.79 (s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H). Yield: 90%. Purity: 89%.

2-Phenyl-4-(4-hydroxyphenyl)-6-(4-methylphenyl)pyrimidine (14b). ^{1}H NMR δ: 3.92 (s, 3H), 6.96 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 7.56−7.59 (m, 3H), 7.84 (s, 1H), 8.10 (d, J = 8.7 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), 8.55−8.57 (m, 2H). Yield: 85%. Purity: 79%.

2-(3-Nitrophenyl)-4-(4-hydroxyphenyl)-6-(4-methylphenyl)pyrimidine (14c). ^{1}H NMR δ: 3.93 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 7.94 (s, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.9 Hz, 2H), 8.35 (dd, J = 1.6, 8.2 Hz, 1H), 9.03 (d, J = 7.8 Hz, 1H), 9.50 (d, J = 1.6 Hz, 1H). Yield: 90%. Purity: 93%.

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