ACS Combinatorial Science

RESEARCH ARTICLE

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Solid-Phase Synthesis of Disubstituted *N*-Acylureas from Resin-Bound Ureas and Acyl Chlorides

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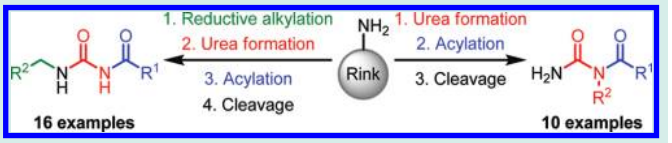
Supporting Information

ABSTRACT: Acylureas (ureides) are valued for their important biological activities. Whereas cyclic acylureas have frequently been the object of solid-phase chemistry, only few reports have focused on the solid-supported preparation of acyclic representatives. We have prepared different types of acylureas on Rink amide resin in three or four steps. The products are either *N*-acylated (**9**, **18**), *N*-acylated-*N*′-alkylated (**10**, **19**), or *N*-acylated-*N*-alkylated (**22**). Characteristic NMR parameters of isomeric acylureas **10**, **19**, and **22** are discussed.



KEYWORDS: acylureas, Rink amide resin, solid-phase synthesis, trimethylsilyl isocyanate

INTRODUCTION

Acylated urea functions are common building blocks of bioactive molecules. Besides cyclic representatives, for example, hydantoins and barbituric acids, which are known for various biological activities and therapeutic applications,[1−4] acyclic *N*-acylureas (ureides) have attracted much attention in medicinal chemistry. Of particular interest among the bioactive acylureas are those bearing the acyl portion of valproic acid (2-*n*-propylvaleric acid) or a related branched acyl moiety.[5−8] For example, tetramethylcyclopropanecarbonylurea (TMC-urea) and dimethylbutanoylurea (DBU) have been considered as promising candidates to become new potent and safe antiepileptic drugs.[9,10]

Besides their anticonvulsant properties, many of those substances showed other central nervous effects, for example, as analgesics or antiarrhythmics.[4,11] Moreover, acylureas were discovered as a novel class of glycogen phosphorylase inhibitors, a molecular target for the control of hyperglycemia in type 2 diabetes.[12,13] Benzoylurea derivatives were also found to exhibit antiproliferative properties in different human tumor cell lines,[14,15] as well as antitumor activity in vivo.[16] Lessene et al. recently reported on the ability of the benzoylurea moiety to mimic α-helices because of the formation of an intramolecular hydrogen bond.[17] The authors anticipated that benzoylureas might therefore serve as inhibitors of interactions between proteins that comprise helical binding epitopes.[17−19]

Various strategies have been reported for the synthesis of ureas on solid support.[2,20−29] Urea formation has been, for example, achieved by reacting primary or secondary amines with resin-bound carbamates,[20,29] isocyanates,[22] or carbamate amides.[23] In the majority of cases, isocyanates were used for the efficient transformation of immobilized amines into ureas.[2,21,24,28] Resin-bound ureas have been frequently utilized as intermediates for the assembly of cyclic acyl ureas, such as hydantoins, on solid support.[2,4,20,21,23,30,31] Another type of cyclic *N*-acylurea, *N*-acyl-benzimidazolinone, was applied as mild acylating agent in the preparation of thioester peptides, which could be generated on Rink or Wang linkers and cleaved from the resin with trifluoroacetic acid.[32] Surprisingly, there are only a few articles on the solid-phase synthesis of acyclic acylureas.[28,33] Ravn et al. reported on the assembly of di- and trisubstituted acylureas on Wang resin from Fmoc amino acids, secondary amines and carboxylic acids in six steps. Resin-bound carbimidoyl chlorides were formed as key intermediates from thioureas by the use of diphenylphosphine dichloride. Next, reaction with carboxylic acids gave *O*-acylisoureas, which subsequently rearranged to the corresponding acylureas.[33]

In continuation of a previous study,[28] we wish to report on different pathways toward disubstituted acyclic acylureas. In the present work on the solid-phase chemistry of acylureas, we started from Rink amide resin, assembled the products in three or four steps using commercially available chemicals, and generated a library of the target molecules.

RESULTS AND DISCUSSION

Our first approach was based on the reaction of three commercially available acyl isocyanates **2**{*1*−*3*} with deprotected Rink amide resin **1** resulting in compounds **9**{*1*−*3*} (Figure 1, Scheme 1, Table 1).[28] A reductive alkylation step was performed before acylurea formation to include a second point of diversity.[34] For this purpose, benzaldehyde **3**{*1*} or 4-methoxybenzaldehyde **3**{*2*} (Figure 2) were condensed with **1** in a mixture of tetrahydrofuran, water, and acetic acid, followed by reduction with sodium cyanoborohydride to form resins **6**. Subsequent reaction with acyl isocyanates **2**{*1*−*3*} led to resin-bound chemsets **8** and the products **10** (Table 1). Mono- and disubstituted acylureas **9** and **10** were obtained in good to excellent yields and high purities after TFA-mediated cleavage and column chromatography. These and following products of this study were characterized by ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, and LC-DAD/MS. With respect to the reactions shown in Scheme 1, the limited

Received: September 28, 2010
Revised: October 10, 2010
Published: November 10, 2010

dx.doi.org/10.1021/co100020b | *ACS Comb. Sci.* 2011, 13, 59–64

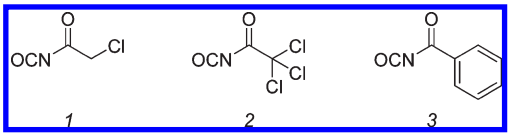
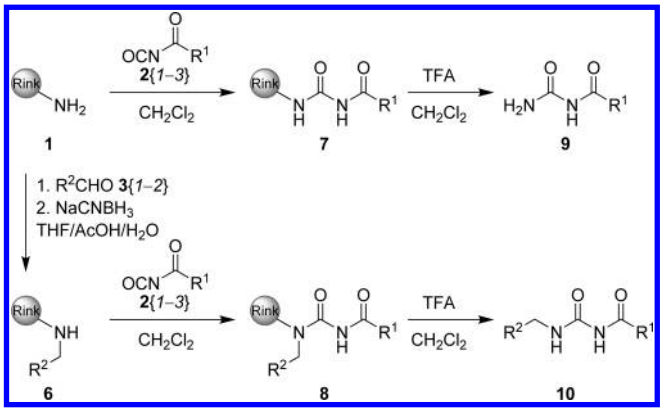


Figure 1. Diversity reagents **2**{*1*−*3*}.

Scheme 1. Preparation of Acylureas 9 and 10 from Resin-Bound Amines 1, 6, and Acyl Isocyanates 2



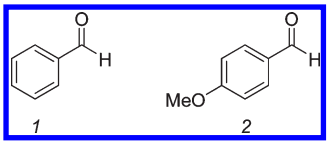


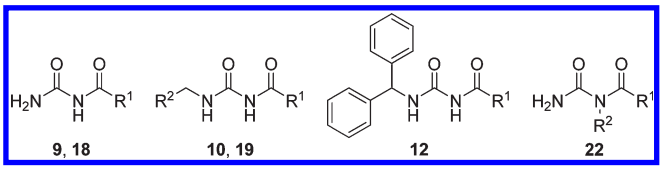
Figure 2. Diversity reagents **3**{*1*−*2*}.

availability and instability[35] of acyl isocyanates constrained the diversity of the acyl residue within the target compounds and prompted us to modify the preparation of acylureas on solid support.

Another approach for the synthesis of *N*-acyl-*N*′-alkylureas in solution comprises the reaction of monosubstituted ureas and carboxylic acids, anhydrides or chlorides.[11,36−39] The preparation of a corresponding unsubstituted urea resin was already established by the reaction of Rink amide resin with trichloroacetyl isocyanate followed by the cleavage of the trichloroacetyl group in refluxing dioxane−water.[28] To avoid high temperatures for the deprotection step, trimethylsilyl isocyanate[40] was used instead of trichloroacetyl isocyanate. After reaction with the corresponding resins **1** or **6**, the trimethylsilyl moiety could be removed by shaking for one hour in a tetrahydrofuran−water mixture (Scheme 2). Depending on the reaction sequence, three urea resins with terminal NH_2 groups were generated, the unsubstituted urea resin **13** and two monoalkylated resin-bound ureas **14**{*1*−*2*} (R^2 = Ph, 4-MeO-Ph). The latter ones were assembled by combining reductive alkylation, reaction with trimethylsilyl isocyanate and deprotection. Accordingly, 4-methoxybenzylurea **15**{*2*} was obtained in 78% yield after cleavage from resin **14**{*2*} (R^2 = 4-MeO-Ph) and purification.

Next, acylation of the urea resins **13** and **14** was investigated. Application of established solution-phase conditions (carboxylic anhydrides, toluene, 80 °C)[11] resulted in the formation of side products, in particular the corresponding carboxylic amides. The underlying expulsion of HNCO might be due to the elevated reaction temperature. Therefore, the solution conditions were modified to be applicable for polymeric support. As can be seen in Schemes 2 and 3, benzhydrylurea **11**[28] was selected to mimic the resin bound urea **13**. Acylation reactions of urea moieties at room temperature have been carried out in pyridine,[36,37] or

Table 1. Acylureas with Corresponding Yields and Purities



entry	scheme	product	R^1	R^2	yield (%)[a]	purity (%)[b]
1	1	**9**{*1*}	CH_2Cl		89	97
2	1	**9**{*2*}	CCl_3		83	100
3	1	**9**{*3*}	Ph		91	100
4	2	**18**{*3*}	$(CH_2)_2Ph$		80	100
5	2	**18**{*4*}	CH=CHPh		78	99
6	2	**18**{*5*}	CH_2OPh		82	95
7	1	**10**{*1*,*1*}	CH_2Cl	Ph	83	96
8	1	**10**{*2*,*1*}	CCl_3	Ph	80	95
9	1	**10**{*3*,*1*}	Ph	Ph	85	94
10	1	**10**{*1*,*2*}	CH_2Cl	4-MeO-Ph	84	95
11	1	**10**{*2*,*2*}	CCl_3	4-MeO-Ph	79	100
12	1	**10**{*3*,*2*}	Ph	4-MeO-Ph	83	97
13	2	**19**{*1*,*1*}	CH_3	Ph	69	100
14	2	**19**{*2*,*1*}	C_2H_5	Ph	65	95
15	2	**19**{*3*,*1*}	$(CH_2)_2Ph$	Ph	68	97
16	2	**19**{*4*,*1*}	CH=CHPh	Ph	66	97
17	2	**19**{*5*,*1*}	CH_2OPh	Ph	70	100
18	2	**19**{*6*,*1*}	4-Me-Ph	Ph	59	99
19	2	**19**{*7*,*1*}	4-Cl-Ph	Ph	45	91
20	2	**19**{*8*,*1*}	2-thienyl	Ph	64	95
21	2	**19**{*1*,*2*}	CH_3	4-MeO-Ph	66	98
22	2	**19**{*2*,*2*}	C_2H_5	4-MeO-Ph	69	100
23	2	**19**{*3*,*2*}	$(CH_2)_2Ph$	4-MeO-Ph	71	99
24	2	**19**{*4*,*2*}	CH=CHPh	4-MeO-Ph	68	95
25	2	**19**{*5*,*2*}	CH_2OPh	4-MeO-Ph	53	100
26	2	**19**{*6*,*2*}	4-Me-Ph	4-MeO-Ph	58	99
27	2	**19**{*7*,*2*}	4-Cl-Ph	4-MeO-Ph	40	95
28	2	**19**{*8*,*2*}	2-thienyl	4-MeO-Ph	54	93
29	3	**12**{*3*}	$(CH_2)_2Ph$		89	100
30	3	**12**{*4*}	CH=CHPh		86	100
31	3	**12**{*5*}	CH_2OPh		89	100
32	3	**12**{*9*}	Ph		92	100
33	4	**22**{*3*,*1*}	$(CH_2)_2Ph$	*n*-Pr	77	93
34	4	**22**{*4*,*1*}	CH=CHPh	*n*-Pr	75	91
35	4	**22**{*5*,*1*}	CH_2OPh	*n*-Pr	82	88
36	4	**22**{*8*,*1*}	2-thienyl	*n*-Pr	79	93
37	4	**22**{*3*,*2*}	$(CH_2)_2Ph$	Bn	72	89
38	4	**22**{*4*,*2*}	CH=CHPh	Bn	83	99
39	4	**22**{*5*,*2*}	CH_2OPh	Bn	79	81
40	4	**22**{*9*,*2*}	Ph	Bn	66	95
41	4	**22**{*4*,*3*}	CH=CHPh	Ph	19	78
42	4	**22**{*9*,*3*}	Ph	Ph	33	85

[a] Yields based on the weight of purified product relative to the initial loading of the resin. [b] Purity determined by HPLC-DAD (see Experimental Section for details).

dx.doi.org/10.1021/co100020b |*ACS Comb. Sci.* 2011, 13, 59–64

organic solvents in the presence of pyridine.[38,39] To retain adequate swelling of the polystyrene resin, we performed the solution reactions to produce *N*-acyl-*N*′-benzhydrylureas **12** (Scheme 3, Table 1) in mixtures of different solvents and pyridine. Dichloromethane−pyridine (9:1) seemed to be suitable for transfer to solid support, as a rapid transformation of **11** with different acyl chlorides was observed. We prepared the resin-bound acylureas **16** from reagent chemset **4** (Figure 3, Scheme 2) and released the final acylureas **18**{*3*−*5*} upon treatment with TFA (Table 1). A similar process resulted in the synthesis of the *N*-acyl-*N*′-alkylureas **19**. These products possess a substituted or unsubstituted benzyl moiety at the one, and an aroyl or alkanoyl group at the other nitrogen. They were obtained in yields between 40 and 71% and purities higher than 90% (Table 1).

In a further attempt, the solid-supported synthesis was envisaged to obtain products through alkylation and acylation at the same nitrogen (Scheme 4). Deprotected Rink amide resin **1** was first reacted with reagent chemset **5** (Figure 4) in dichloromethane, followed by conversion with reagent chemset **4** (Figure 3), using the acylation conditions noted above. With the exception of the *N*-phenylureas **22**{*4,3*} and **22**{*9,3*}, these acylureas **22** were obtained in good yields (Table 1). Structural characterization of the products revealed that the terminal and not the internal nitrogen of urea resins **20** was acylated to indeed produce *N,N*-disubstituted derivatives **22**. A limit in our approach was observed as follows: When reacting the alkylated resin **6** (Scheme 2) with isocyanates **5** (similar to Scheme 4), the resulting urea resins could not be successfully acylated. Instead of the desired acylureas, disubstituted ureas were obtained after cleavage (data not shown). Thus, the introduction of a third point of diversity into the target structure failed.

With the two series of isomeric acylureas, i.e., compounds **10** and **19**, as well as **22**, in hand, we determined indicative NMR parameters for both regioisomers. The characteristic chemical shifts for representatives **19**{*5,1*} and **22**{*5,2*} are depicted in Figure 5. On the one hand, the ^{1}H NMR spectra of *N*-acyl-*N*′-alkylureas showed a doublet at ∼4.4 ppm for the benzylic protons and two distinct signals for the NH protons. The signals for the benzylic and the urea carbonyl carbons appear at ∼43 ppm and 153 ppm, respectively. On the other hand, the singlets for the benzylic protons of *N*-acyl-*N*-alkylureas are shifted downfield to ∼5.0 ppm, and the signal for two NH protons arises at ∼7.6 ppm. A relative shift of benzylic and urea carbonyl carbons to lower field (∼46 and 155 ppm, respectively) was also observed.

In summary, various routes to acylureas from Rink amide resin were developed. Key steps of the syntheses were combined to obtain different disubstituted acylureas. For *N*-acyl-*N*′-alkylureas

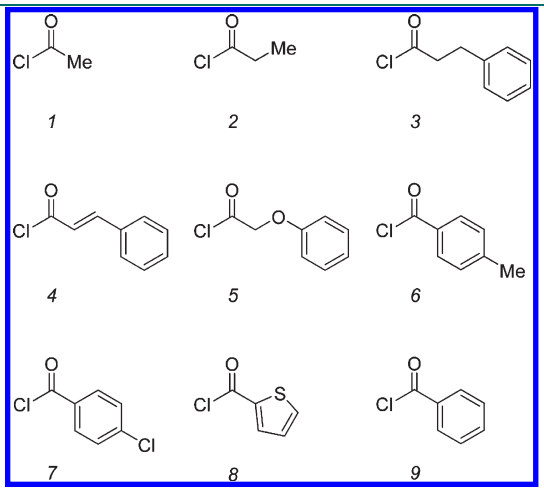
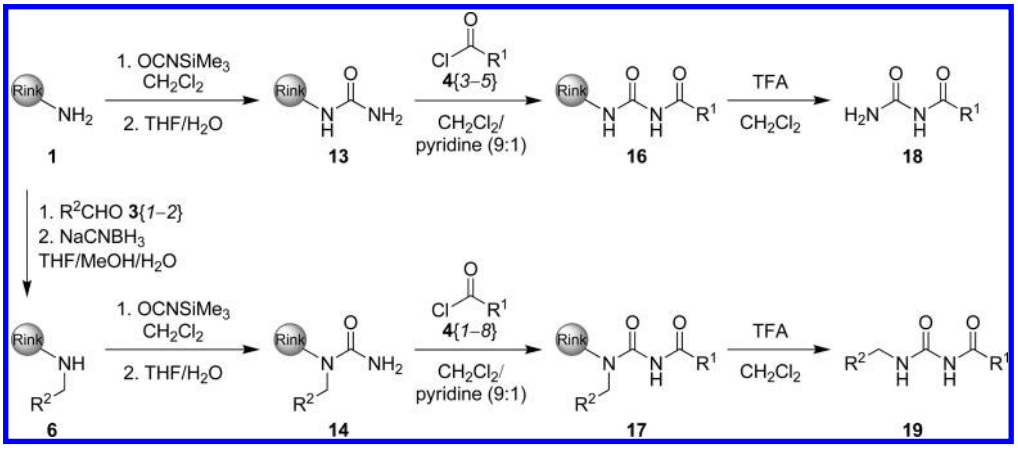
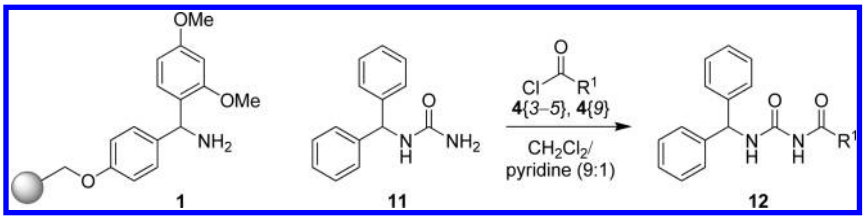


Figure 3. Diversity reagents **4**{*1*−*9*}.

Scheme 2. Preparation of Acylureas 18 and 19 from Resin-Bound Ureas 13, 14, and Acyl Chlorides 4



Scheme 3. Deprotected Rink Amide Resin (1, Left) and Synthesis of *N*-acyl-*N*′-benzhydrylureas 12 in Solution (Right)



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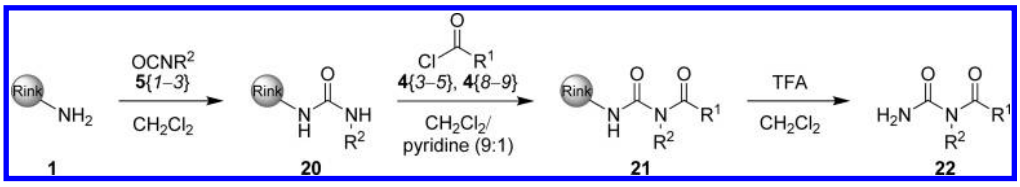
Scheme 4. Preparation of *N*-Acyl-*N*-alkylureas 22 from Corresponding Resin-Bound Ureas 20 and Acyl Chlorides 4



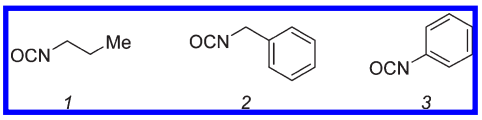


Figure 4. Diversity reagents **5**{*1*−*3*}.

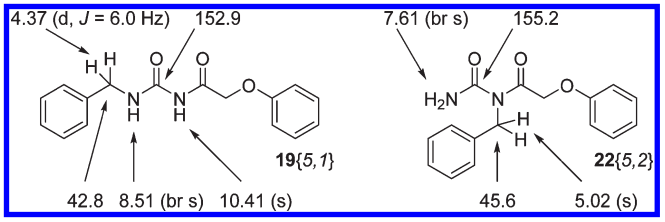


Figure 5. Comparison of selected ^{1}H and ^{13}C NMR chemical shifts (ppm) from regioisomers **19**{*5,1*} and **22**{*5,2*}.

these are (i) reductive alkylation, (ii) a novel trimethylsilyl isocyanate-promoted formation of a urea moiety, and (iii) acylation using acyl chlorides in dichloromethane/pyridine at room temperature. *N*-acyl-*N*-alkylureas were generated by (i) urea formation with different isocyanates and (ii) acylation with acyl chlorides. Thus, a library of potentially bioactive acylureas was generated and characteristic structural parameters were assigned to regioisomeric products.

EXPERIMENTAL PROCEDURES

Fmoc Removal. Fmoc-protected Rink amide resin (695 mg, 0.50 mmol) was deprotected with 20% piperidine in DMF (10 mL) at rt. After 1 h, the resin was washed with DMF, CH_2Cl_2, MeOH, and CH_2Cl_2 (3× 10 mL each) and dried to give the deprotected resin **1**.

Cleavage. The resin was swollen in CH_2Cl_2 (10 mL). After removal of the solvent, cleavage of the material from the resin was performed using CH_2Cl_2−TFA 9:1 (10 mL) for 1 h at rt, followed by washing with CH_2Cl_2 (2 × 5 mL). After the filtrates were combined, the solution was concentrated in vacuo and purified by column chromatography as described below. Cleavage of resins **7** and **16** followed by column chromatography (CH_2Cl_2−MeOH, 19:1) gave the corresponding *N*-acylureas **9** and **18**, respectively. Cleavage of resins **8** and **17** followed by column chromatography (CH_2Cl_2−MeOH, 29:1) gave the corresponding *N*-acyl-*N*′-alkylureas **10** and **19**, respectively. Cleavage of resins **21** followed by column chromatography (CH_2Cl_2−MeOH, 29:1) gave the corresponding *N*-acyl-*N*-alkylureas **22**.

General Procedure for the Reductive Alkylation: Synthesis of Resin 6. Reductive alkylation was performed according to Brown and Nuss.[34] AcOH (0.5 mL) and H_2O (0.5 mL) were added to a mixture of resin **1**, THF (10 mL) and the appropriate aromatic aldehyde **3** (0.60 mmol, 1.2 equiv). After shaking for 5 min at rt, $NaCNBH_3$ (31 mg, 0.50 mmol) was added and the mixture was shaken for further 3 h. The resin was washed with THF, H_2O, MeOH, CH_2Cl_2, and MeOH (2×10 mL each) and dried in vacuo to give resin **2**.

General Procedure for the Preparation of Acylurea Resins 7 and 8. Resins **1** or **6** were treated with a mixture of the appropriate acyl isocyanate **2** (5.0 mmol, 10 equiv) in dry CH_2Cl_2 (10 mL) at rt. After they were shaken for 2 h, the reaction solutions were removed and the resins were washed with CH_2Cl_2, THF, MeOH, CH_2Cl_2, and MeOH (2× 10 mL each).

General Procedure for the Synthesis of Urea Resins 13 and 14. The appropriate amine resin **1** or **6** was reacted for 2 h at rt with a solution of trimethylsilyl isocyanate (576 mg, 5.0 mmol, 10 equiv) in dry CH_2Cl_2 under nitrogen atmosphere. Then, the solvent was removed, the resin resuspended in THF−H_2O (10 + 2 mL) and shaken for 1 h, followed by washing with CH_2Cl_2, THF, MeOH, CH_2Cl_2, and MeOH (2× 10 mL each).

General Procedure for the Preparation of Urea Resins 20. Deprotected Rink amide resin **1** was allowed to react with the appropriate isocyanate **5** (5.0 mmol, 10 equiv) dissolved in dry CH_2Cl_2 for 2 h at rt. Washing was performed with CH_2Cl_2, THF, MeOH, CH_2Cl_2, and MeOH (2× 10 mL each), and the corresponding resin **20** was dried.

General Procedure for the Acylation on Solid Support: Synthesis of Resins 16, 17, or 21. Urea resins **13**, **14**, or **20** were put in a solution of the appropriate acyl chloride **4** (2.5 mmol, 5 equiv) in dry CH_2Cl_2−pyridine 9:1 (10 mL) and shaken overnight at rt. The reaction mixtures were filtered, and the resins were washed with CH_2Cl_2, DMF, THF, MeOH, CH_2Cl_2, and MeOH (2× 10 mL each) and dried in vacuo.

General Procedure for the Solution-Phase Synthesis of Benzhydryl Derivatives 12. A solution of the appropriate acyl chloride **4** (0.60 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a mixture of benzhydrylurea **11**[28] (113 mg, 0.50 mmol), CH_2Cl_2 (4 mL) and pyridine (1 mL) at rt. Progress of the reactions was controlled by TLC. After complete consumption of **11** (1−5 h), the reaction mixture was concentrated in vacuo and purified by column chromatography (CH_2Cl_2−MeOH, 50:1).

ASSOCIATED CONTENT

Supporting Information. General methods and materials, compound characterization, and ^{1}H and ^{13}C NMR spectra of all compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The authors are grateful to H. Passgang, A. Reiner, M. Schneider, S. Terhart-Krabbe, and I. Kretschmer for assistance. This work has been supported by the German Research Foundation (GRK 804).

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