JOURNAL OF combinatorial CHEMISTRY

Report

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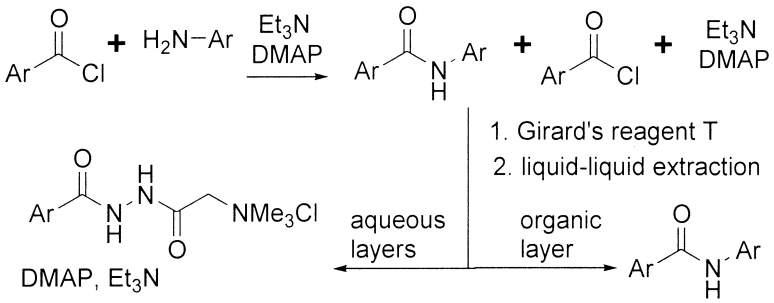
J. Comb. Chem., **2002**, 4 (6), 549-551• DOI: 10.1021/cc020044z • Publication Date (Web): 28 September 2002



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Solution-Phase Synthesis of a Library of Biaryl Amides Using Girard's Reagent T as an Acid Chloride Scavenger

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Received June 24, 2002

Introduction

Solution-phase synthetic techniques offer many advantages over solid-phase approaches, such as unlimited scale, easy manipulation, and reduction in validation time. Recently, solution-phase chemistry for library generation has been receiving increased attention as a lead discovery and optimization tool in drug discovery.[1] However, with solution-phase syntheses, the rapid purification or isolation of desired compounds from a reaction mixture is difficult and has proved a bottleneck in the synthetic process. As a result, many innovative purification approaches have been disclosed, and their progress has been well-reviewed.[1a]

Since amide linkages are a common structural motif in many drug molecules, several solution-phase approaches for the generation of amide libraries have been developed.[1a] For example, Boger employed a general liquid−liquid extraction process with acid and base for purification of single compound libraries.[2] The water-soluble coupling reagents, such as BOP and EDCI, have been employed for easy purification.[2,3] A water-soluble base, 1,1,3,3-tetramethylguanidine, was utilized to catalyze the reaction and trap the generated acid.[4] A small amino acid, potassium sarcosinate, has been used as a quencher to remove excess electrophiles by generating water-soluble byproducts.[5] More recently, a water-soluble quarternary ammonium salt bearing three amino functional groups was used to remove electrophiles.[6] Other approaches utilizing polymer-supported reagents or resins have also been reported.[1b,c] Suto found ion-exchange resins were useful as reagents and scavengers in syntheses.[7] Parlow used polymeric reagents in syntheses to generate reactive species and to remove unreacted or derivatized starting materials from reaction mixtures.[8]

Screening of our compound collection, based on measuring the ability of test compounds to inhibit melanin production, led to the identification of compound **1**, containing an amide linkage between two aromatic groups (Figure 1). As part of our drug discovery efforts, to develop a rapid structure−activity relationship exploration and optimization program, we were confronted with the task of generating focused libraries based on compound **1**. Herein, we describe a novel strategy, utilizing Girard's reagent T (**2**, (carboxymethyl)trimethylammonium chloride hydrazide) as an electrophile scavenger, for the synthesis of biaryl amide analogues.

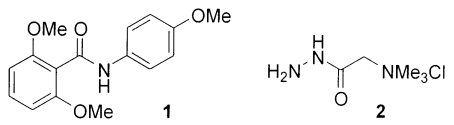
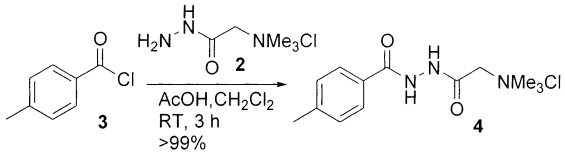


Figure 1. Structures of compound **1** and Girard's Reagent T (**2**).

Scheme 1



Results and Discussion

Our attempts to generate amide libraries began with the water-soluble coupling reagents, such as BOP and EDCI, for the formation of an amide bond between an aromatic acid and an arylamine. After the reaction, the mixtures were purified employing standard liquid−liquid extraction processes with acids and bases. However, this approach did not provide the amides in sufficient yields or with adequate purities, presumably because of the low reactivities of arylamines. For this reason, we used aromatic acid chlorides instead of aromatic acid/coupling reagents to obtain satisfactory yields. The reaction of an arylamine with a slight excess of an acid chloride in the presence of triethylamine and a catalytic amount of DMAP resulted in the complete conversion of the arylamine to the appropriate amide. Addition of a small amount of water to the reaction followed to transform any unreacted acid chloride to the corresponding acid for the typical aqueous extraction. However, the hydrolysis of the aromatic acid chlorides to the carboxylic acid was acknowledged to be very sluggish and required several days to complete. Some aromatic acid chlorides were very difficult to hydrolyze to their corresponding carboxylic acids,[7a] and their removal by liquid−liquid extraction was sometimes unsatisfactory.

To circumvent these problems, we utilized Girard's reagent T (**2**) as an acid chloride scavenger. Girard's reagent T has mainly been used to separate lipophilic ketones and aldehydes from impurities via their water-soluble hydrazone derivatives.[9] We previously used Girard's reagent T to remove excess aromatic aldehydes from mixtures in a solution-phase stilbene library synthesis.[10] However, as far as we know, the condensation of Girard's reagents with acid chlorides has not been reported. Therefore, we needed to investigate the reaction conditions to explore the potential of Girard's reagent T as an acid chloride scavenger. After considerable effort, it was found that the aromatic acid chloride **3** in CH_2Cl_2 could be converted to its water-soluble hydrazine derivative **4** on treatment with a solution of the Girard's reagent T (**2**) in AcOH at room temperature in excellent yield (99%), as shown in Scheme 1.

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10.1021/cc020044z CCC: $22.00
Published on Web 09/28/2002

Scheme 2. Solution-Phase Biaryl Amide Library Production Route

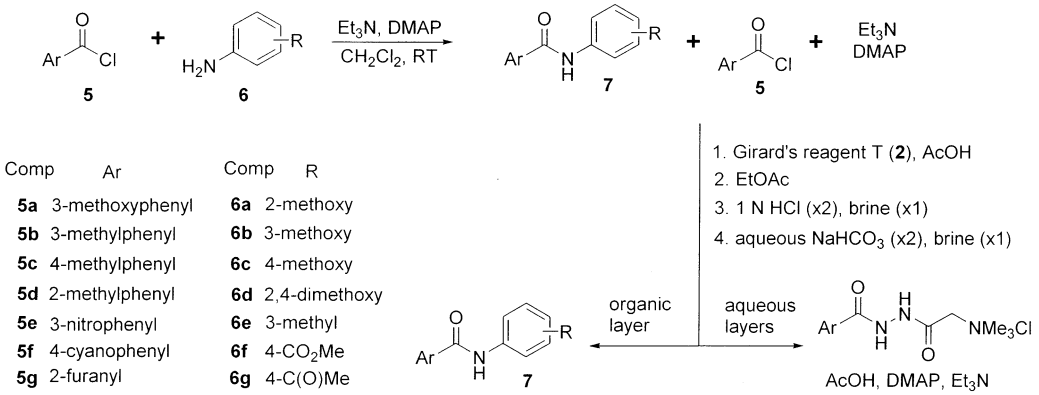


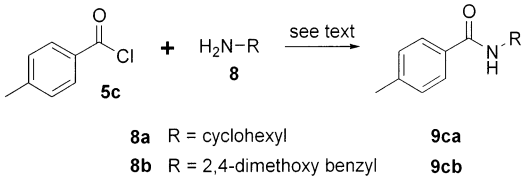
Table 1. Solution-Phase Synthesis of Biaryl Amides

entry	acid chloride **5**	amine **6**	reaction condition[a]	amide **7**	yield (%)	purity[b] (%)
1	**5a**	**6a**	A	**7aa**	95	99
2	**5a**	**6b**	A	**7ab**	93	98
3	**5a**	**6c**	A	**7ac**	92	97
4	**5a**	**6d**	A	**7ad**	90	95
5	**5a**	**6e**	A	**7ae**	93	96
6	**5b**	**6c**	A	**7bc**	91	94
7	**5b**	**6d**	A	**7bd**	91	96
8	**5c**	**6a**	A	**7ca**	95	98
9	**5c**	**6b**	A	**7cb**	95	98
10	**5c**	**6c**	A	**7cc**	93	97
11	**5c**	**6d**	A	**7cd**	94	98
12	**5d**	**6c**	A	**7dc**	92	95
13	**5d**	**6d**	A	**7dd**	94	96
14	**5e**	**6b**	A	**7eb**	92	95
15	**5f**	**6b**	A	**7fb**	92	97
16	**5g**	**6b**	A	**7gb**	92	99
17	**5b**	**6f**	A	**7bf**	62	96
18	**5b**	**6f**	B	**7bf**	93	98
19	**5a**	**6f**	B	**7af**	91	94
20	**5a**	**6g**	B	**7ag**	93	99
21	**5b**	**6g**	B	**7bg**	95	96

[a] The reaction was run using 1.5 equiv of **5** for 5 h (condition A) or 3.0 equiv of **5** for 3 days (condition B); for details, see text. [b] Determined by HPLC (Phenomenex Luna 5u C18 column, 4.6 mm × 250 mm; ultraviolet absorption detector at 225 nm; isocratic, MeOH/H_2O = 25:75, 40 min).

To demonstrate the potential of Girard's reagent T as a scavenger (Scheme 2), selected arylamines **6** (0.2 mmol) in 1 mL of CH_2Cl_2 were intentionally treated with an excess of various aromatic acid chlorides **5** (1.5 equiv) in the presence of triethylamine (2.0 equiv) and a catalytic amount of DMAP (0.1 equiv).[11] The mixture was stirred for 5 h, after which a solution of Girard's reagent T (**2**) in AcOH (0.5 M, 0.5 mL) was added. The resulting mixture was stirred overnight at room temperature and then diluted with ethyl acetate (3 mL). The reaction mixture was purified by subsequent washing with 1 N HCl (2 mL × 2), brine (2 mL), saturated aqueous $NaHCO_3$ (2 mL × 2), and brine (2 mL). The organic layers were passed through a short pad of drying agent (Na_2SO_4) and evaporated to yield the final products **7**. All of the products were checked by HPLC and ^{1}H NMR and were essentially pure, as shown in Table 1. In all cases (entries 1−17, Table 1), the resulting amides were free from byproducts and possible impurities. In general, the arylamines, with electron-donating groups on the aromatic ring, gave excellent yields (entries 1−16, Table 1). However, the yield of the amide **7bf** was low (entry 17, Table 1), possibly due to the incomplete conversion of the arylamine **6f**, which has an electron-withdrawing group, to its corresponding amide in a given reaction time. This problem could be overcome by using a longer reaction time (3 days) and excess acid chloride (3 equiv) to drive this reaction to completion (entries 18−21, Table 1). It is noteworthy that the yields of the amide **7ag** and **7bg**, which have a ketone functional group, were also excellent (entries 20−21, Table 1). This result implies that Girard's reagent T does not condense with the possibly reactive ketone group of the products in the reaction condition described.

Scheme 3



In addition, simple alkylamines, such as cyclohexylamine (**8a**) and 2,4-dimethoxy benzylamine (**8b**) were then reacted with the aromatic acid chloride **5c** under the same conditions (5 h, 1.5 equiv of acid chloride) and were found to provide the corresponding products (**9ca** and **9cb**) in excellent yields (93% and 99%, respectively) and purities (>97%) after employing the purification procedure described above (Scheme 3).

After establishing a protocol for the efficient generation of the amide libraries, we wanted to see how effective this methodology would be in building libraries containing mixtures. As a model study, five different amines (**6b**, **6c**, **6d**, **8a**, and **8b**), having dissimilar reactivities, were employed. An excess of the aromatic acid chloride **5c** (1.5 equiv) was added to a mixture of equimolar amounts of five amines (0.1 mmol each) in CH_2Cl_2 in the presence of triethylamine (2.0 equiv) and a catalytic amount of DMAP (0.1 equiv). The use of excess aromatic acid chloride was needed to ensure the complete conversion of the amines to the corresponding amides. When total consumption of the amines was observed by GC and TLC, the reaction mixture was treated with a solution of Girard's reagent T in AcOH. After employing the workup procedure described above, the purity of the library and the presence of each of the desired components were confirmed by HPLC, GC, and ^{1}H NMR.

The resulting library contained approximately equal amounts of all five amide members (**7cb**, **7cc**, **7cd**, **9ca**, and **9cb**) in the range of 19−21% each, with a total content of 97% purity.

In summary, we have demonstrated the utility of Girard's reagent T in the solution-phase generation of amide libraries. Girard's reagent T, an inexpensive scavenger, was found to be very efficient in trapping excess acid chlorides to give water-soluble byproducts, which could be readily removed from the products by liquid−liquid extractive workup. Because our approach employed acids for purification, the amide libraries in which the products contain the acid labile functional groups might not be efficiently built. However, the ease of use and the excellent purity of the amide libraries obtained are important features of this protocol.

Acknowledgment. This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (HMP-00-CH-15-0014).

Supporting Information Available. Experimental procedures and analytical data for compounds **4**, **7** and **9**; copies of ^{1}H NMR spectra of compounds **4**, **7** and **9**; GC and HPLC data of the mixture library of 5 compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC020044Z