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Versatile and Efficient Solid-Phase Syntheses of Pyrazoles and Isoxazoles

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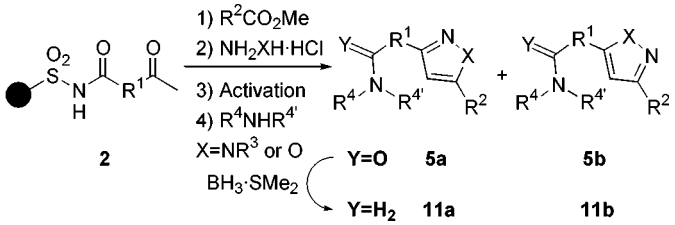
ABSTRACT



Condensation of aromatic or aliphatic esters with resin-supported acetyl carboxylic acids 2, followed by cyclization with hydrazines or hydroxylamine, activation of the linker, and cleavage using amines provides highly substituted, isomeric pyrazoles or isoxazoles 5. This general method gives products in excellent yields and purities in which the ratio of the two isomers can be easily controlled. A variation of this scheme generates 1,4,5- and 1,3,4-trisubstituted pyrazoles and related isoxazoles. Post-cleavage reduction with borane converts pyrazole amides to amines such as 11.

Many heterocyclic compounds have interesting biological activities. Pyrazoles and isoxazoles figure prominently in this regard.[1] The recent success of a pyrazole COX-II inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry.[2] The past few years have also witnessed explosive developments in combinatorial chemistry and solid-phase synthesis. We were interested in preparing some highly substituted pyrazoles and isoxazoles on solid support. A literature survey turned up a few reports on the subject.[3] However, these methods were not sufficiently versatile for our purpose. Therefore, we set out to develop an alternative route to pyrazoles and isoxazoles on solid support. Herein we report our solid-phase syntheses of 1,3,5-, 1,4,5-, and 1,3,4-trisubstituted pyrazoles and related isoxazoles.

The general approach to pyrazoles and isoxazoles by Marzinzik and Felder[3a] starts with aromatic keto-acids on Rink-amide resin. Condensation with aromatic esters affords 1,3-diketones. Alkylation of this 1,3-diketone followed by ring-closure with hydrazines or hydroxylamine gives pyrazoles or isoxazoles on the resin. Acidic cleavage provides products bearing a primary amide group. We were mainly interested in pyrazoles and isoxazoles containing substituted amides. The flexibility of initiating the sequence using aliphatic keto-acids was also very important to us. We hoped to introduce diversity at the amide site by using safety-catch resins. Unexpectedly, this also allowed us to use aliphatic keto-acids as starting materials. Scheme 1 shows the general outline of our approach. The acetyl carboxylic acid can be loaded onto an aryl sulfonamide safety-catch resin **1** with in situ generated anhydride using 1,3-diisopropylcarbodiimide (DIC) in the presence of diisopropylethylamine (DIEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP). The use of the methyl ketones ensures a high degree of regio-

(1) For example, there are 2292 pyrazoles and 906 isoxazoles in the MDL Drug Report (MDDR-3D, 99.2), representing 3.0% of entries. They are 1.6% of entries in Comprehensive Medicinal Chemistry (CMC-3D 99.1). Both databases are from MDL Information Systems.

(2) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.

(3) (a) Marzinzik, A. L.; Felder, E. R. *Tetrahedron Lett.* **1996**, *37*, 1003. (b) Cody, D. R.; DeWitt, S. H.; Hodges, J. C.; Roth, B. D.; Schroeder, M. C.; Stankovic, C. J.; Moos, W. H.; Pavia, M. R.; Kiely, J. S. WO 94/08711, 1994.

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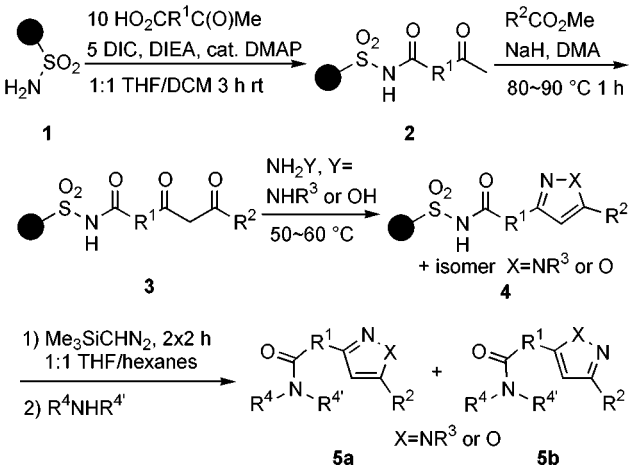
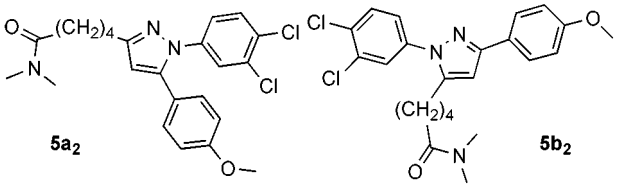
Scheme 1. General Synthesis of 1,3,5-Trisubstituted Pyrazoles and Related Isoxazoles



selectivity during the subsequent condensation to generate 1,3-diketones **3**.[4] Cyclization using hydrazines or hydroxylamine gives isomeric heterocycles **4**. The resin linker can be activated by (trimethylsilyl)diazomethane. Cleavage with primary or secondary amines affords **5a** and **5b** in high yields and purities.[5]

Initially, we used literature conditions for the pyrazole cyclization.[3a] For many aromatic ester substrates, this gives an isomeric ratio of **5a**:**5b** well in excess of 10:1. We felt that this was not suitable for mixture libraries we intended to prepare because expected changes in that ratio among different substrates would mask the true SAR from the minor isomers. Therefore, factors influencing the ratio of isomers **5a** and **5b** were further investigated using various cyclization conditions during the preparation of $\mathbf{5a_2}$ and $\mathbf{5b_2}$. The results are presented in Table 1. If the hydrazine hydrochloride was used without DIEA, the cyclization gave 2−3:1 ratios of isomeric pyrazoles. Methanol gave closer to equal ratios than dimethylacetamide (DMA) as the solvent. There is a small but consistent leveling of ratios when concentrated sulfuric acid is added. However, other acids such as phosphoric acid and trifluoroacetic acid did not show such an effect. At room temperature in methanol, the reactions were slightly more selective for $\mathbf{5a_2}$ (data not shown). However, the rates were too slow to be practical without the addition of DIEA. In the absence of additives, this roughly 2:1 ratio holds for the majority of about 70 esters we have tried in this cyclization using hydrazine hydrochlorides. Sterically hindered benzoates were the exceptions. For example, 2-fluoro- and 2-methoxybenzoates gave about 2:1 isomeric mixtures while the slightly bulkier 2-methylbenzoate gave at least a 10:1 ratio of **5a** to **5b**.[6] Steric hindrance during the hydrazone formation appears to control the regiochemistry.

Table 1. Factors Influencing Pyrazole Isomer Ratios[a]



solvent	additive[b]	$\mathbf{5a_2}$/$\mathbf{5b_2}$ ratio[c]	purity (%)[d]
MeOH	none	1.9	88
MeOH	30% H_2SO_4	1.6	89
MeOH	30% H_3PO_4	2.6	87
MeOH	100% DIEA	~50	89
DMA	none	3.0	90
DMA	30% H_2SO_4	2.6	95
DMA	30% H_3PO_4	3.8	96
DMA	100% DIEA	~75	91

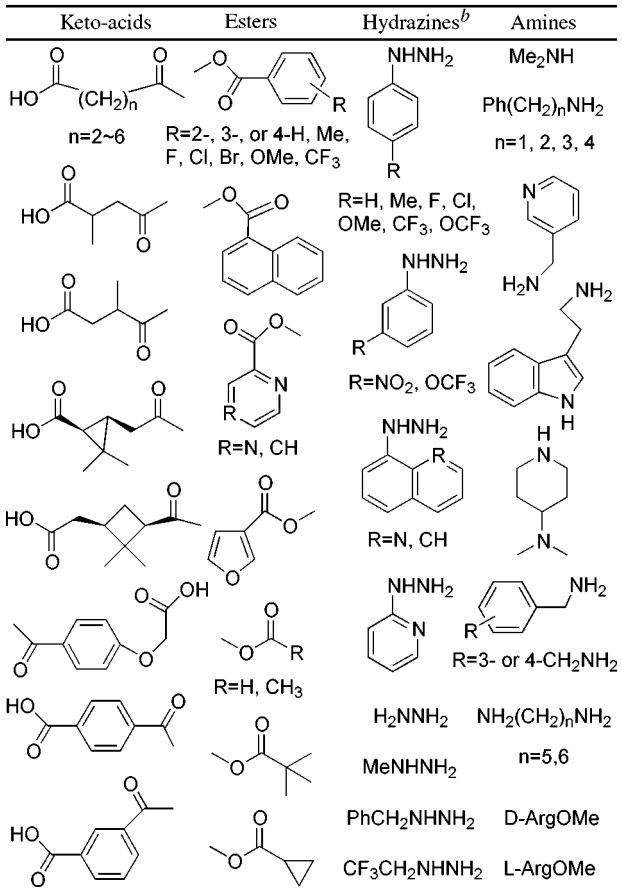
[a] Results of runs leading to products $\mathbf{5a_2}$ and $\mathbf{5b_2}$ using general conditions outlined in footnote 5 except for the additive used during cyclization at 50 °C. [b] Added as mol % of the hydrazine·HCl. Sulfuric acid and phosphoric acid used were 98% and 85%, respectively. [c] Ratios determined by HPLC. NMR and LC/MS gave very similar ratios in cases checked. [d] Combined area of product HPLC peaks.

(4) No regioisomers were observed as a result of the condensation step for aromatic esters. Lower aliphatic esters, especially formates, gave both regioisomers at this step as was observed in similar reactions in solution.

(5) **Representative procedure:** To 1.02 g of 4-sulfamylbenzoyl AM resin (NovaBiochem, 1.15 mmol/g), 34 mg of DMAP, and 1.197 g (9.2 mmol) of 4-acetylbutyric acid in a 20-mL SPE cartridge were added 8 mL of 1:1 THF/DCM and 0.80 mL (4.6 mmol) of DIEA. After mixing, 0.72 mL of DIC (4.6 mmol) was added and the resulting mixture was agitated at room temperature for 5.5 h. The reaction mixture was drained. The resin was washed with 3 × 15 mL each of 1:1 DCM/THF, MeOH, DMF, MeOH, and 6 × 15 mL DMA to give **2** ($R^1 = (CH_2)_3$). Ten percent of this resin was transferred into another 20-mL SPE cartridge and washed with 3 × 5 mL of DMA. Methyl *p*-anisate (0.482 g, 2.90 mmol), 0.125 g of a 60% NaH oil dispersion (3.1 mmol), and 1 mL of DMA were added. It was heated in a 80 °C oven for 1 h after mixing. The cartridge was taken out of the oven briefly three times during the first half hour and shaken. After draining the reaction mixture, the resin was washed with 15 mL of DMA and ice cold 4:1 HOAc/water alternatively three times, followed by 3 × 15 mL each of THF, DMF, and MeOH to give resin **3** ($R^1 = (CH_2)_3$, $R^2 = 4\text{-MeOC}_6H_4$). 3,4-Dichlorophenylhydrazine hydrochloride (246 mg, 1.15 mmol), 19 μL of concentrated sulfuric acid, and 3 mL of MeOH were added to the resin. The mixture was heated at 50 °C for 19 h and drained. The resin was washed with 4 × 15 mL of MeOH, DMF, and THF to give pyrazoles **4** ($R^1 = (CH_2)_3$, $R^2 = 4\text{-MeOC}_6H_4$, X = N-3,4-$Cl_2C_6H_3$). This resin was treated with 1.0 mL of 2 M (trimethylsilyl)diazomethane in hexanes and 0.8 mL of THF for 2 h twice. After draining the reaction mixture, the resin was washed with 4 × 15 mL each of THF, MeOH, and THF. After adding 0.54 mL of a solution from 148 mg (1.15 mmol) of 4-dimethylaminopiperidine in 1.9 mL dioxane, the resulting mixture was heated at 50 °C for 19 h. After cooling to room temperature, 600 mg of methylisocyanate polystyrene resin (NovaBiochem, 0.42 mmol/g) and 2 mL of THF were added. After 6 h, the filtrate was collected from the reaction mixture. The resin was washed with 3 × 3 mL of MeOH and combined with the filtrate to afford crude $\mathbf{5a_1}$ and $\mathbf{5b_1}$. RP-HPLC showed 2:1 isomers at 81% purity (LC/MS: M + H = 515.3). Semipreparative HPLC on a C18 column using 35−45% MeCN in water with 0.5% TFA gave 14.7 mg of $\mathbf{5a_1}$ and 7.9 mg of $\mathbf{5b_1}$ after lyophilization (20% and 11% as TFA salt; $R^1 = (CH_2)_3$, $R^2 = 4\text{-MeOC}_6H_4$, X = N-3,4-$Cl_2C_6H_3$, $R^4R^{4'}N$ = 4-dimethylaminopiperidin-1-yl). ^{1}H NMR $\mathbf{5a_1}$ (CD_3OD, 500 MHz): δ 7.51 (d, 8.4 Hz, 1H), 7.50 (d, 2.6 Hz, 1H), 7.15−7.18 (m, 2H), 7.12 (dd, 8.4 and 2.6 Hz, 1H), 6.91−6.94 (m, 2H), 6.41 (s, 1H), 4.71−4.77 (m, 1H), 4.15−4.19 (m, 1H), 3.80 (s, 3H), 3.44 (tt, 3.9 and 12.1 Hz, 1H), 3.10−3.16 (m, 1H), 2.86 (s, 6H), 2.75 (t, 7.5 Hz, 2H), 2.61−2.67 (m, 1H), 2.52−2.55 (m, 2H), 2.07−2.12 (m, 2H), 2.00−2.06 (m, 2H), 1.61−1.69 (m, 1H), 1.51−1.59 (m, 1H). ^{1}H NMR $\mathbf{5b_1}$ (CD_3OD, 500 MHz): δ 7.77 (d, 2.6 Hz, 1H), 7.73−7.76 (m, 2H), 7.70 (d, 8.4 Hz, 1H), 7.50 (dd, 8.6 and 2.4 Hz, 1H), 6.95−6.98 (m, 2H), 6.67 (s, 1H), 4.65−4.70 (m, 1H), 4.03−4.09 (m, 1H), 3.82 (s, 3H), 3.42 (tt, 3.7 and 12.1 Hz, 1H), 3.04−3.10 (m, 1H), 2.84 (s, 6H), 2.81 (t, 7.6 Hz, 2H), 2.56−2.62 (m, 1H), 2.43−2.47 (m, 2H), 2.05−2.09 (m, 2H), 1.89−1.98 (m, 2H), 1.55−1.63 (m, 1H), 1.46−1.54 (m, 1H). COSY and NOESY spectra unambiguously assigned the isomers.

The conditions given are applicable to a variety of substrates. Table 2 lists some representative examples. With

Table 2. Representative Substrates Used Successfully in Scheme 1 for Pyrazole and Isoxazole Syntheses[a]



[a] Not in all possible combinations. [b] In addition to hydroxylamine hydrochloride.

minor modifications, the scope of this scheme can be expanded further. For aliphatic carboxylic acids, loading to resin can be done at room temperature in about 3 h.[7] Typically, 10 equiv of acid are used. However, we have employed as few as 6 equiv without lowering yield or purity. For aromatic acids such as 3- and 4-acetylbenzoic acids, we have used 4-pyrrolidinopyridine instead of DMAP. These reactions are conducted at 50 °C. Double coupling is used (overnight and 3 h) to ensure complete loading. However, 2-acetylbenzoic acid gives low yields of final products even under these conditions.

Condensations of esters with resin **2** are typically carried out using 20−30 equiv of ester and 10−20 equiv of NaH in concentrated DMA. No attempts have been made to determine the limiting amount of esters required. The reactions with alkyl methyl ketones can be done at 80 or 90 °C in about 1 h. Condensations involving aryl methyl ketone require the higher temperature. Repeating this condensation reaction offers no advantage in yield or purity of the final products. Aliphatic esters react well in our scheme, in contrast to the previous procedure.[3a]

Six to ten equivalents of aryl hydrazines are usually employed during cyclization of resin **3**. In addition to aryl hydrazines, hydrazine or alkyl hydrazines can also be used. However, they only react well as salts. For example, 2−3 equiv of hydrazine monohydrochloride gives the best results among several salt forms examined. Hydrazine or alkyl hydrazine free bases or salts in the presence of DIEA give no products upon cleavage. Under these conditions, it appears that the more nucleophilic alkyl hydrazines cleave substrate prematurely from the resin linker during the cyclization step. Therefore, in the absence of strong base, the safety-catch linker appears unstable to nucleophiles such as the free base form of hydrazine or alkyl hydrazines. Hydroxylamine hydrochloride behaves like alkyl hydrazines during cyclization, giving isomeric isoxazoles. Adding DIEA during these cyclizations resulted in no products being formed during cleavage for isoxazoles.

The safety-catch linker in **4** is generally activated by double treatments with 10 equiv of (trimethylsilyl)diazomethane in 1:1 hexanes/THF.[7] However, there are cases where Mitsunobu alkylation[7,8] is more advantageous. For example, when the parent hydrazine was used during cyclization to give N−H pyrazoles, (trimethylsilyl)diazomethane activation resulted in isomeric methyl pyrazoles in addition to the expected N−H pyrazoles. Mitsunobu conditions also gave better results when the aromatic carboxylic amides were cleaved from the resin. No attempts have been made to reduce the treatments or the amount of reagents in the activation step.

Reactive amines such as dimethylamine in large excess and high concentration can cleave to give final products **5** at ambient temperature. Typically, 1.5 equiv of amine (versus resin loading) in a minimal amount of solvent such as THF or DMA covering the resin will cleave the product at 50 to 80 °C overnight. As expected, amides with α-substitution require more vigorous conditions.

Excess nonvolatile amines in the crude products can be removed simply by scavenging with isocyanate or thioisocyanate resin. In cases where that is not suitable, the products can be purified using RP-HPLC. Isomeric products are often separable under proper conditions.

Variations of Scheme 1 can produce pyrazoles and isoxazoles with different substitution patterns. Scheme 2 shows one of these variations. The products are 1,4,5- and 1,3,4-trisubstituted pyrazoles and the corresponding isoxazoles. The ratio **10a**/**10b** is typically about 5−10:1.

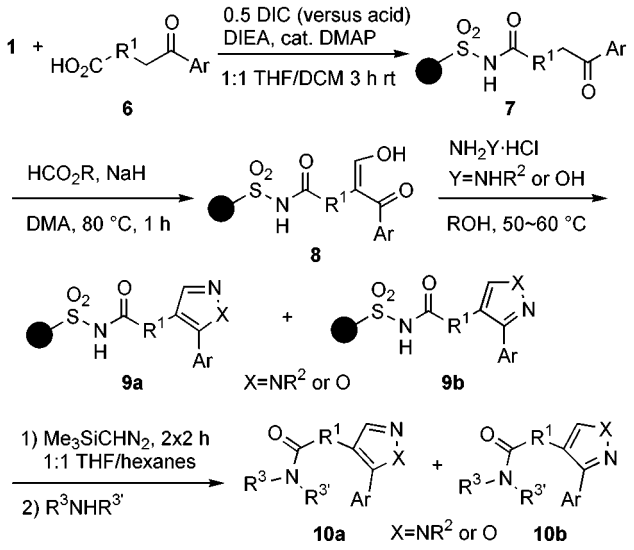
The diversity of products from these general schemes can be increased further by post-cleavage transformations. One simple post-cleavage transformation that produces pure products is borane reduction of amides to amines.[9] Applica-

(6) These isomers have characteristic UV profiles. 1,4-Diaryl-3-alkyl pyrazoles **5a** have a peak at about 260−265 nm while the 1,3-diaryl-5-alkyl isomers **5b** have a peak at 275 nm or above.

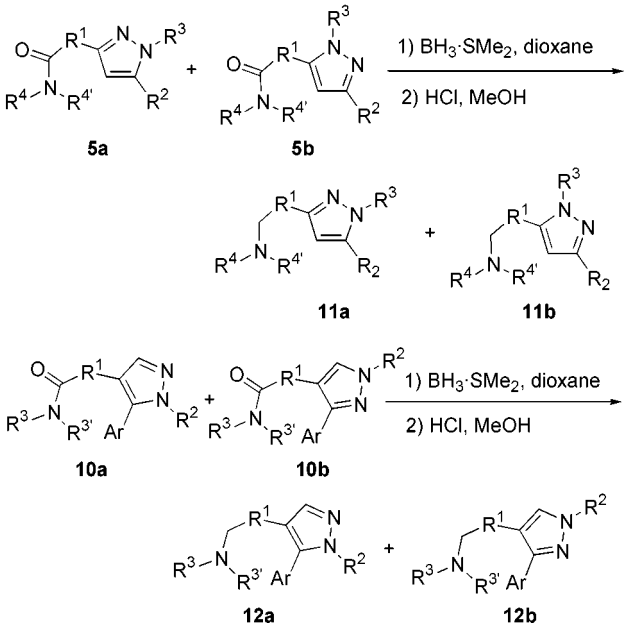
(7) Willoughby, C. A.; Chapman, K. T. Unpublished results.

(8) We used 20 equiv each of pentafluorobenzyl alcohol, triphenylphosphine, and diisopropyl azodicarboxylate in 1:1 DCM/THF at 0.4 M and ambient temperature for 3 h.

Scheme 2. General Synthesis of 1,4,5-and 1,3,4-Trisubstituted Pyrazoles and Related Isoxazoles



Scheme 3. Post-Cleavage Reduction of Amides to Amines



tion of this methodology to our systems gives the corresponding pyrazole amines **11** and **12** from pyrazoles amides **5** and **10** as illustrated in Scheme 3.[10,11] This not only increases the diversity of products obtainable but also gives a more desirable functional group in the context of medicinal chemistry.

In summary, we have discovered versatile and efficient solid-phase syntheses of 1,3,5-, 1,4,5-, and 1,3,4-trisubstituted pyrazoles and the related isoxazoles in high yields and purities. Our schemes expand the scope of solid-phase pyrazole and isoxazole synthesis by employing both aliphatic and aromatic keto-acids, esters, and hydrazines in the sequence. The ability to use a variety of amines to cleave the heterocycles from resin adds further versatility to this procedure. The ratio of pyrazole isomers can be controlled to some extent by varying the reaction conditions. A simple post-cleavage reduction with borane converts the pyrazole amides into amines in high yields and purities. These procedures provide ready access to well over 10^9 compounds from commercially available starting materials.

Acknowledgment. We thank Dr. Christopher A. Willoughby for providing conditions developed for loading similar carboxylic acids on safety-catch resins and for activating the resin, Mr. Steven M. Hutchins for sharing conditions for reducing amides to amines, and Dr. Nathan Yates for LC/MS data.

Supporting Information Available: Proton NMR of compounds **5a$_1$** and **5b$_1$** and COSY and NOESY spectra for compound **5b$_1$**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006197H

(9) Hutchins, S. M.; Chapman, K. T. Unpublished results.

(10) Isoxazoles were not stable under these conditions.

(11) Reduction of **5a$_3$** to **11a$_1$** is illustrative (R^1 = $(CH_2)_4$, R^2 = 4-$MeOC_6H_4$, R^3 = 4-MeC_6H_4, and R^4 = $R^{4'}$ = Me). Pyrazole amide **5a$_3$** (0.0376 mmol, 19.0 mg, TFA salt) was treated with 0.4 mL of 0.5 M BH_3·SMe_2 in 1,4-dioxane at 50 °C for 3 h. After removing solvent and excess reagent under vacuum, 3.5 mL of 1% HCl in MeOH was added and the mixture heated at 50 °C overnight. The residual after removing solvent under vacuum was dissolved in 3.5 mL of 1% HCl in MeOH and evaporated under vacuum again. This dissolution and evaporation process was repeated once with 1% HCl in MeOH and once with MeOH alone. HPLC showed 96% pure **11a$_1$** confirmed by LC/MS (M + H = 378.5). Lyophilization from 3:7 MeCN/water gave 15.4 mg of **11a$_1$**·2HCl (91%).