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An alumina-catalyzed Michael addition of mercaptans to *N*-anilinomaleimides and its application to the solution-phase parallel synthesis of libraries

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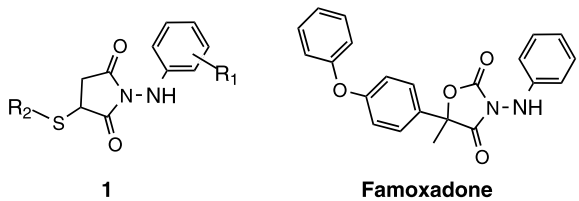
Abstract—A novel strategy for the synthesis of 3-sulfanylsubstituted 1-(arylamino)-pyrrolidine-2,5-dione derivatives via the alumina-catalyzed Michael addition of mercaptans to *N*-anilinomaleimides is described. The utilization of alumina in the synthesis offers important advantages such as good yields, convenience and mild conditions.

Several very mild and highly selective organic transformations have been achieved on the surface of alumina.[1] For example, epoxide ring opening,[2] elimination reactions[3] and conjugate additions[4] have been reported. Alumina induced intramolecular additions of hydroxyl groups to carbonyl conjugated double bonds have been reported,[5] but no comparable alumina promoted intermolecular additions of alcohols or mercaptans to α,β-unsaturated carbonyl compounds have been observed. We report herein an alumina-catalyzed intermolecular Michael addition of mercaptans to *N*-anilinomaleimides. Michael additions of thiols to α,β-unsaturated carbonyl compounds are important reactions in organic synthesis.[6]

Famoxadone, a new agricultural fungicide, is a member of the oxazolidinone fungicides (Fig. 1).[7] As part of our discovery effort toward new agricultural fungicides, we are interested in the synthesis of 3-sulfanylsubstituted 1-(arylamino)-pyrrolidine-2,5-dione derivatives **1** (Fig. 1). Although numerous derivatives originated from the parent oxazolidinone heterocycle have been synthesized, the corresponding 3-sulfanylsubstituted 1-(arylamino)-pyrrolidine-2,5-dione derivatives have not been evaluated until hitherto. Our synthetic strategy is outlined in Scheme 1. The preparation of *N*-aminomaleimides has been reported.[8] The key step of the synthesis is the Michael addition of mercaptans to *N*-aminomaleimides.



1 **Famoxadone**

Figure 1. General structure of the 3-substitutedsulfanyl-1-(arylamino)pyrrolidine-2,5-dione derivatives **1** and the known fungicide Famoxadone.

The *N*-aminomaleimides were prepared from maleic anhydride and the corresponding hydrazines in a two-step one-pot reaction. The Michael addition of mercaptans to *N*-alkylmaleimides has been reported.[9] However, under those conditions reaction of either benzenethiol or mercaptoacetic acid with *N*-anilinomaleimide gave very low yields of the Michael addition product. Later we found that the Michael addition of mercaptans to *N*-aminomaleimides was achieved in good yields in the presence of neutral alumina (Aldrich-activated, neutral, Brockman I, standard grade, 150 mesh). In the absence of alumina, the reaction gave very low yields of products and many side products were formed. The surface of alumina probably induced the polarization of the C–O bond for the Michael addition. Alumina has also been reported to catalyze a Michael addition of secondary amines to exocyclic α,β-unsaturated ketones.[10] Attempts to extend this reaction to amines were unsuccessful. Treatment of *N*-anilinomaleimides with amines afforded 1-aryl-2-(3-carboxyamideacryloyl)-hydrazines (Scheme 2) in good yields.

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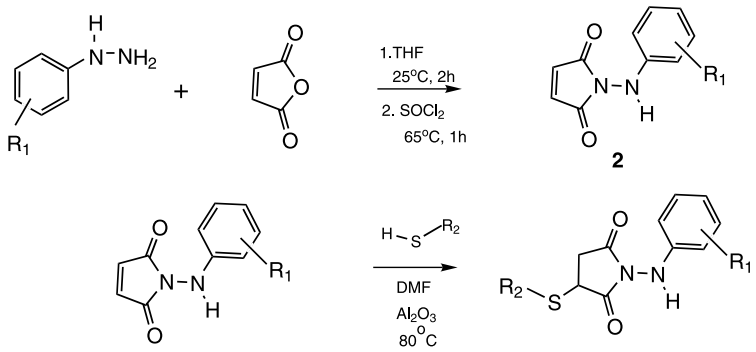
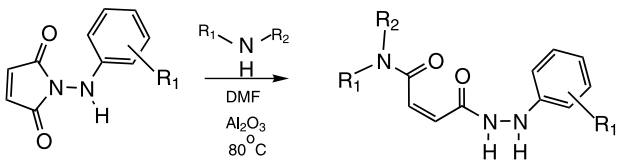


Scheme 1.



Scheme 2.

A rapid solution-phase parallel synthesis was developed based on this methodology and used to synthesize a 300 member library. A set of 10 *N*-(arylamino)-maleimides were prepared from maleic anhydride and the corresponding hydrazines.[11] All products were obtained as colored crystalline solids with an average yield of 62% (Table 1). A set of 30 commercially available mercaptans were selected for the Michael addition step (Table 2). The parallel synthesis were then performed in an 10×30 array of 13×125 mm screw-cap tubes.[12] All final compounds were purified using a reverse phase HPLC system and were analyzed by HPLC and mass spectrometry. 200 Compounds were obtained in greater than 85% purity in multimilligram quantitities.

In conclusion, the utilization of alumina in the synthesis of the title compounds offers important advantages such as good yields, convenience and mild conditions. The solution-phase parallel synthesis of libraries provides a practical and efficient methodology for the rapid synthesis of the title compounds. This method is general and flexible and could be used to make very large libraries. The structural properties of these derivatives may provide important leads as agricultural fungicides.

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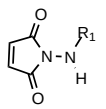
Table 1. *N*-Arylaminomaleimide intermediates prepared for library synthesis



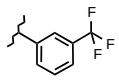
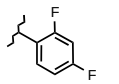
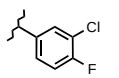
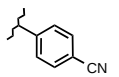
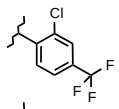
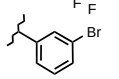
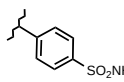
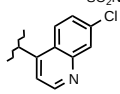
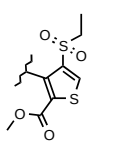
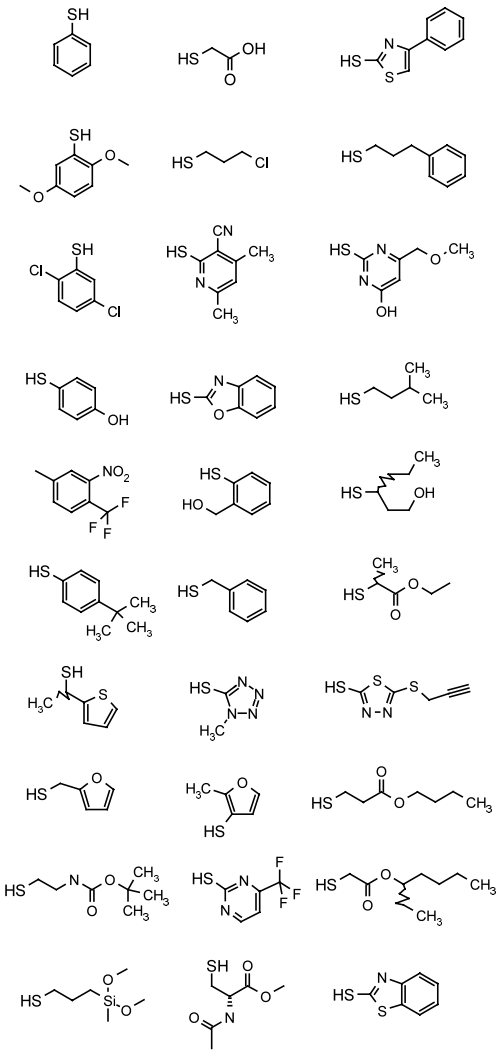
No.	R_1	Isolated Yield(%)
1a		60
1b		43
1c		69
1d		61
1e		58
1f		68
1g		67
1h		23
1i		98
1j		81

Table 2. Thiols used for Michael addition step



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11. Example procedure: ***N*-anilinomaleimide(2a)**: Maleic anyhydride (5.0 g, 51.0 mmol) was dissolved in anhydrous THF (100 mL) and phenylhydrazine (5.5 g, 5.0 mL, 51.0 mmol) was added in an N_2 atmosphere. The yellow solution was stirred for 2 h at room temperature. Thionyl chloride (7.3 g, 4.5 mL, 61.2 mmol) was then added to the mixture over 2 min. The reaction was then heated to 65°C over 30 min and stirred for an additional 30 min at 65°C. The resulting brown mixture was allowed to cool and concentrated in vacuo to give a dark-brown oily solid. Minimal dry EtOH was added to create a thick suspension. The solid was vacuum filtered and washed twice with dry EtOH. The resulting orange crystalline solid was dried overnight in vacuo to yield ***N*-anilinomaleimide(2a)** (6.0 g, 63%, >95% pure by LC/MS), mp 145–148, ^{13}C NMR (DMSO-d_6, 300 MHz) δ 113.284, 119.698, 121.046, 129.115, 140.838, 143.698, 167.014; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.55 (d, 1H, $J=3.0$ Hz), 6.89–6.86 (m, 1H), 7.28–7.24 (m, 4H), 7.79 (d, 1H, $J=3.0$ Hz); $C_{10}H_8N_2O_2=188.19$; MS: $[M+H]^+=189$.
12. Example procedure: **3-phenylsulfanyl-1-phenylamino-pyrrolidine-2,5-dione ($1,R_1,R_2=$Ph)**: *N*-Anilinomaleimide(I) (0.037 g, 0.2 mmol) was dissolved in distilled DMF (1 mL) and benzenethiol (0.066 g, 0.6 mmol) was added. Neutral alumina (0.110 g) was added and the mixture was stirred at 80°C for 1 h. Mixture was allowed to cool and was filtered through a 0.2 micron filter to remove the alumina. The resulting solution was then directly injected onto a reverse phase HPLC purification system and purified. Pure fractions were collected and concentrated in vacuo to yield **3-phenylsulfanyl-1-phenylamino-pyrrolidine-2,5-dione ($1,R_1,R_2=$Ph)** as a white solid (0.039 g, 66%, 99% pure by LC/MS), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.78 (dd, 1H, $J=4.3$ Hz and $J=4.1$ Hz), 3.23 (dd, 1H, $J=9.2$ Hz and $J=9.1$ Hz), 4.05 (dd, 1H, $J=9.1$ Hz and $J=4.2$ Hz), 6.53–7.53 (m, 10H); $C_{16}H_{14}N_2O_2S=298.37$; MS: $[M+H]^+=299$.