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LETTER

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Silica-Supported Aluminum Chloride-Assisted Solution Phase Synthesis of Pyridazinone-Based Antiplatelet Agents

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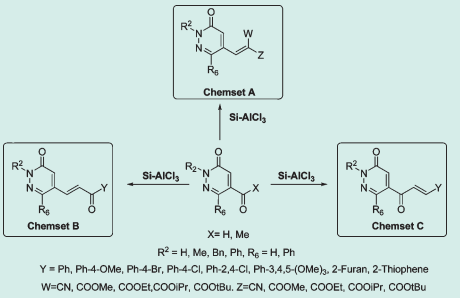
Supporting Information

ABSTRACT: A solution phase protocol that enabled the synthesis of three diverse libraries of pyridazin-3-ones incorporating α,β-unsaturated moieties at position 5 of the heterocyclic core has been developed using silica-supported aluminum trichloride as a heterogeneous and reusable catalyst. This robust procedure has facilitated the *hit to lead* process for these series of compounds and allowed the identification of new potent derivatives that elicit antiplatelet activity in the low micromolar range.



KEYWORDS: supported reagents, Knoevenagel and Claisen−Schmidt condensations, platelet aggregation inhibitors, chalcones, solution phase synthesis

Contemporary Organic Synthesis is faced with the challenge of developing new, efficient, atom economical, and eco-friendly processes that enable the preparation of diverse structures in a rapid and cost-effective manner.[1] While solid phase organic synthesis has been the method of choice for the production of large libraries since the early days of combinatorial chemistry, solution phase synthesis has recently gained importance, particularly in the context of the parallel synthesis of focused libraries. Solution phase library generation has been fuelled by the development of successful concepts such as solid-supported reagents, catalysts, and scavengers. Indeed, this approach has emerged as the leading strategy for library generation because it combines the advantages of both solid phase organic synthesis and solution phase chemistry (e.g., the ease of monitoring the progress of the reactions by liquid chromatography-mass spectrometry (LC-MS), thin layer chromatography (TLC), or standard NMR techniques).[2] In addition to its efficacy and robustness, a major requirement of novel supported reagents concerns their reusability, a factor that has significant environmental and economic impact since the most costly components in a chemical reaction are often not the starting materials but the catalyst.[3]

Knoevenagel and Claisen−Schmidt condensations occupy a prominent position within the carbon−carbon bond formation synthetic armamentarium,[4−6] with both transformations catalyzed by a wide range of highly diverse reagents.[7,8] The development of novel heterogeneous catalytic systems for these reactions is a highly active research area. Advances in this field not only increase the reliability and general interest of these transformations, but more importantly have enabled the implementation of environmentally friendly synthetic methods.[9] Both transformations are widely documented to be reliable and useful in the synthesis of fine chemicals,[8] hetero Diels−Alder reactions,[10] and particularly in the preparation of compounds of biological significance.[11]

In the context of a Medicinal Chemistry program,[12,13] we recently reported the discovery of novel families of potent platelet aggregation inhibitors derived from the pyridazin-3-one scaffold and incorporating diverse α,β-unsaturated residues at position 5 of the heterocycle (Figure 1). It was found that compounds derived from chemotypes A, B, and C (Figure 1) elicited the highest antiplatelet activity, with the regioisomeric chemotypes B and C being particularly attractive since they can be considered as pyridazinone/chalcone hybrid structures. We describe here the development of a silica-supported aluminum chloride-assisted solution phase protocol that enables the synthesis of focused libraries derived from previously identified chemotypes. A preliminary account of the pharmacological data obtained during this process is also presented.

Knoevenagel and Claisen−Schmidt condensations have proven successful with a highly diverse set of catalysts and experimental conditions (e.g., diverse bases, Lewis acids, non-conventional thermal sources and supported reagents), but these experimental protocols are generally not readily amenable to the parallel approach. In the context of a program aimed at optimizing previously identified hit structures (Figure 1), it was necessary to develop an efficient, robust, and simple experimental protocol that would be capable of delivering libraries of the target chemotypes. These requirements led to the choice of aluminum chloride as a reagent as it is superior to

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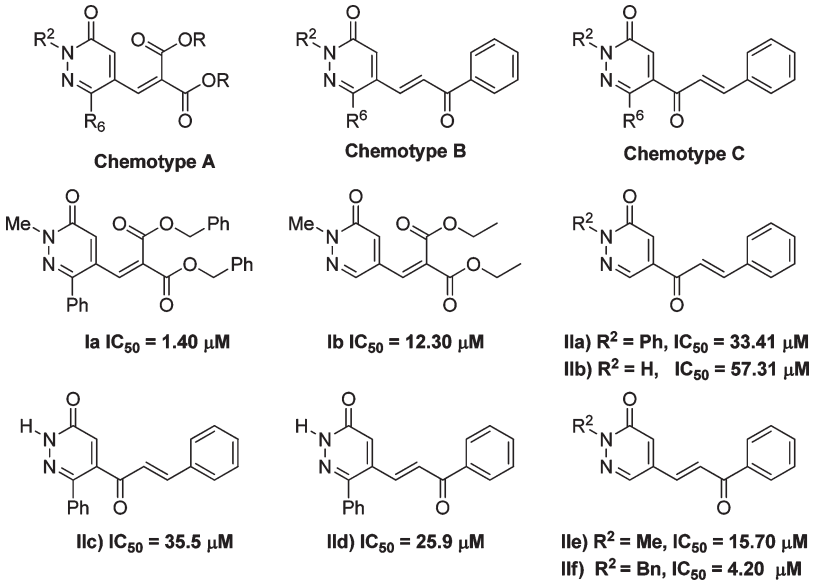

Figure 1. Representative pyridazin-3-ones as platelet aggregation inhibitors.

established preparative methods in both the Knoevenagel and the Claisen−Schmidt transformations, and results were experimentally validated during the early phases of the project.[13] In spite of the excellent reactivity profile observed, several drawbacks that are usually associated with the use of this reagent were experienced. For example, aluminum chloride readily undergoes hydrolysis when exposed to moisture, tends to dimerize when dissolved, and often forms a suspension of $Al(OH)_3$ during reaction workup. It was therefore decided to evaluate the applicability of polymer-supported aluminum chloride (e.g., Si−$AlCl_3$) during the synthesis of target arrays. In comparison with conventional aluminum chloride, the silica-bound equivalent offers several advantages over the free catalyst[14] (e.g., a milder acidity, superior shelf life, and the ability to conduct non-aqueous work-ups)[15] or the polystyrene-supported version (such as no swelling and ability to carry out reactions in polar solvents). Accordingly, for library production purposes the use of Si−$AlCl_3$ was assessed. The preparative applications of this reagent have been reported previously, and it proved to be particularly effective in Friedel−Crafts alkylations and acylations[16] and in ether synthesis.[17] To the best of our knowledge, however, the application of this material as a catalyst in Knoevenagel and Claisen−Schmidt condensations remains unexplored.

The synthetic pathways developed to access the target pyridazinone arrays are based on the assembly of the exocyclic α,β-unsaturated framework through either the Knoevenagel (chemotype A) or the Claisen−Schmidt (chemotypes B or C) condensations (Scheme 1), with silica-supported aluminum chloride employed as a catalyst. The synthetic strategy and building blocks employed were both designed to achieve our aim of preparing a diverse library to enable the preliminary assessment of the structural determinants for antiplatelet activity in these series (e.g., electronic, steric, and lipo-/hydrophilic features). Thus, the reactive groups [e.g., formyl (**A1**−**6**) or acetyl (**B1**−**6**)] present in the heterocyclic precursors were readily transformed into the corresponding α,β-unsaturated system (Scheme 1) by reaction with a diverse range of activated methylene compounds (**C1**−**8**), acetophenones (**D1**−**8**), or carboxaldehydes (**E1**−**8**). Optimized experimental conditions for the three libraries (chemotypes A−C) are given in Scheme 1.

The 5-formylpyridazinones **A1** and **A4** and activated methylene compounds **C1** and **C4** were selected as model substrates for process optimization during the preliminary study into the synthesis of chemotypes A. The main experimental parameters explored were the catalyst ratio [catalytic (0.1 or 0.4 equiv) vs stochiometric conditions], the solvent (THF, MeCN, dioxane, or EtOH) and the temperature (25−120 °C). Preliminary investigations identified the optimal conditions for the Knoevenagel reactions on the tested substrates, with the use of EtOH as solvent at 110 °C and 0.4 equiv of Si-$AlCl_3$ found to give the best results. These conditions were used for library production starting from building blocks **A** and **C**. A remarkable feature of these conditions concerns robustness, as the required 5-alkylidene pyridazinones were successfully obtained regardless of the reactivity profile of the starting malonate partners (i.e., **C4**−**C8**) (Table 1).

Two representative 5-formylpyridazinones (**A1**, **A4**) and 5-acetylpyridazinones (**B1**, **B4**), as well as benzaldehyde (**E1**) and acetophenone (**D1**), were employed as model substrates for the synthesis of libraries of chemotypes B and C (Tables 2, 3). As for the Knoevenagel reaction, the catalyst ratio [catalytic (0.1 or 0.4 equiv) vs stochiometric conditions], solvents (dioxane, tetrahydrofuran (THF), EtOH, and dimethylformamide (DMF)) and temperatures (25−120 °C) were assessed. Preliminary screening highlighted the critical influence that the solvent and temperature had on the reaction behavior. The optimal solvent was found to be ethanol for compounds of chemotype B and dioxane for the regioisomeric series (chemotype C). Satisfactory yields were obtained on working at 80 and 110 °C, respectively. The use of higher temperatures (>100 °C) during the synthesis of enones B led to side reactions.

The screening of the optimal catalyst ratio during the study of the Claisen−Schmidt condensation on 5-formyl- or 5-acetylpyridazin-3-ones incorporating a methoxymethyl group at position 2 of the heterocyclic core (e.g., **A6** and **B6**, Scheme 1, Tables 2, 3) provided additional evidence for the robustness of this versatile reagent (Scheme 1). Thus, it was verified that, in clear contrast to the results obtained on employing aluminum chloride, the use of a large excess (up to 10 equiv) of the supported Lewis acid afforded

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Scheme 1. Synthesis of Target Pyridazin-3-one Libraries[18]

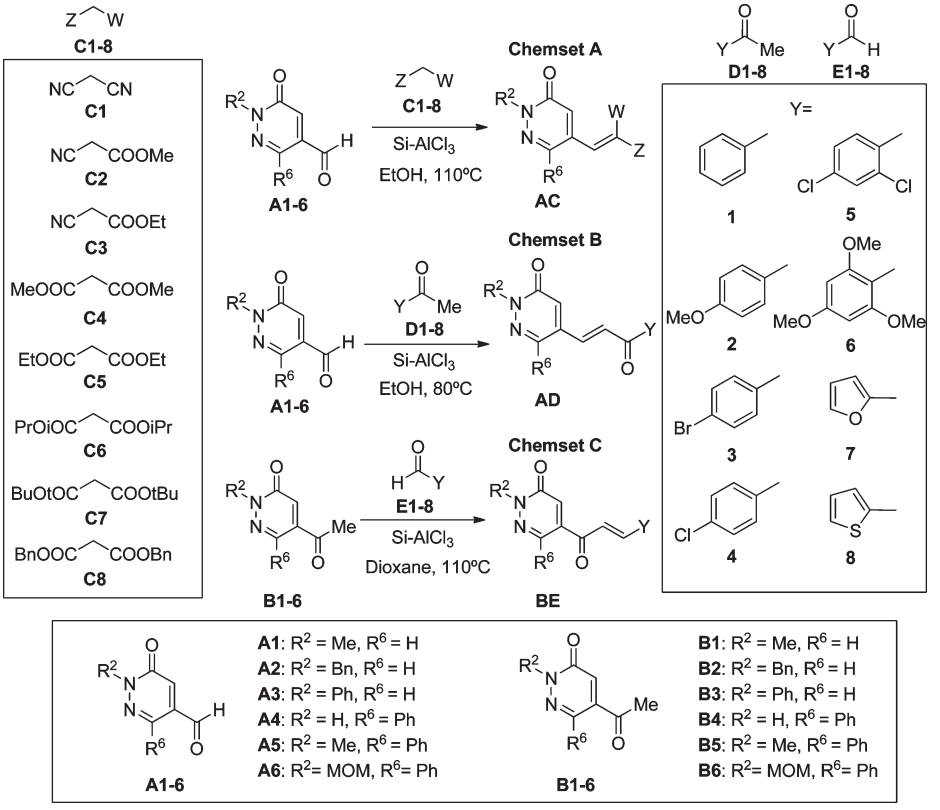
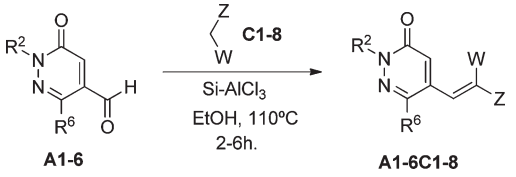


Table 1. Structures and Isolated Yields of Representative Knoevenagel-Type Compounds



cmpd	R^2	R^6	W	Z	yield (%)	cmpd	R^2	R^6	W	Z	yield (%)
A1C1	Me	H	CN	CN	87	**A4C1**	H	Ph	CN	CN	80
A1C4	Me	H	COOMe	COOMe	60	**A4C3**	H	Ph	CN	COOEt	82
A1C5	Me	H	COOEt	COOEt	68	**A4C5**	H	Ph	COOEt	COOEt	74
A1C7	Me	H	COO^tBu	COO^tBu	86	**A4C6**	H	Ph	COO^iPr	COO^iPr	76
A1C8	Me	H	COO^tBn	COO^tBn	85	**A4C7**	H	Ph	COO^iBu	COO^iBu	72
A2C1	Bn	H	CN	CN	86	**A5C5**	Me	Ph	COOEt	COOEt	78
A2C4	Bn	H	COOMe	COOMe	64	**A5C3**	Me	Ph	CN	COOEt	87
A2C5	Bn	H	COOEt	COOEt	77	**A5C4**	Me	Ph	COOMe	COOMe	67
A2C6	Bn	H	COO^iPr	COO^iPr	66	**A5C6**	Me	Ph	COO^iPr	COO^iPr	88
A2C7	Bn	H	COO^tBu	COO^tBu	68	**A5C7**	Me	Ph	COO^tBu	COO^tBu	88

the target structures without promoting cleavage of the methoxymethyl protecting group. In addition to the catalytic efficacy observed during the Knoevenagel and Claisen−Schmidt condensations, a remarkable feature of the synthetic protocol documented here concerns the recyclability of silica-supported aluminum chloride. Once the reaction had finished, the polymer-supported reagent was separated from the reaction mixture by filtration, submitted to a washing protocol (dioxane, CH_2Cl_2, diethyl ether), and then dried under vacuum for 12 h. The recovered polymeric material was routinely reused (at least three times) during library production without significant loss of activity and with the average yield maintained within the series for substrates of similar reactivity (e.g., **A2D1**: 54%, **A4D1**: 55% and **B1E1**: 50%, **B2E1**: 55%, **B4E1**: 56%).

Preliminary biological data from thrombin-induced aggregation studies on human platelets[19] performed on representative

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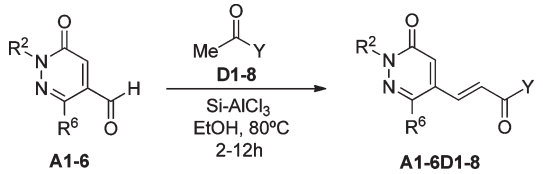
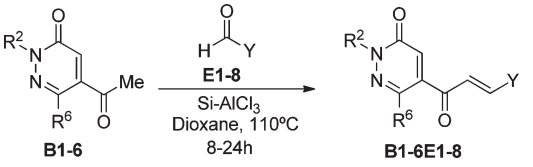
Table 2. Structures and Isolated Yields of Representative 1-Aryl-3-(2,6-substituted-3-oxo-pyridazin-5-yl)-2-propen-1-ones



cmpd	R^2	R^6	Y	yield (%)	cmpd	R^2	R^6	Y	yield (%)
A1D1	Me	H	Ph	57	**A3D2**	Ph	H	Ph-4-OMe	58
A1D2	Me	H	Ph-4-OMe	56	**A3D3**	Ph	H	Ph-4-Br	55
A1D3	Me	H	Ph-4-Br	55	**A3D4**	Ph	H	Ph-4-Cl	57
A1D4	Me	H	Ph-4-Cl	60	**A3D5**	Ph	H	Ph-2,4-Cl	60
A1D5	Me	H	Ph-2,4-Cl	58	**A3D6**	Ph	H	Ph-3,4,5-$(OMe)_3$	62
A1D6	Me	H	Ph-3,4,5-$(OMe)_3$	56	**A3D7**	Ph	H	2-Furyl	54
A1D7	Me	H	2-Furyl	54	**A3D8**	Ph	H	2-Thienyl	56
A1D8	Me	H	2-Thienyl	57	**A4D1**	H	Ph	Ph	62
A2D1	Bn	H	Ph	58	**A4D2**	H	Ph	Ph-4-OMe	46
A2D2	Bn	H	Ph-4-OMe	52	**A4D3**	H	Ph	Ph-4-Br	56
A2D3	Bn	H	Ph-4-Br	58	**A4D4**	H	Ph	Ph-4-Cl	57
A2D4	Bn	H	Ph-4-Cl	58	**A4D5**	H	Ph	Ph-2,4-Cl	50
A2D5	Bn	H	Ph-2,4-Cl	57	**A4D6**	H	Ph	Ph-3,4,5-$(OMe)_3$	58
A2D6	Bn	H	Ph-3,4,5-$(OMe)_3$	60	**A4D7**	H	Ph	2-Furyl	51
A2D7	Bn	H	2-Furyl	52	**A4D8**	H	Ph	2-Thienyl	59
A2D8	Bn	H	2-Thienyl	54	**A5D1**	Me	Ph	Ph	68
A3D1	Ph	H	Ph	56	**A6D1**	MOM	Ph	Ph	68

Table 3. Structures and Isolated Yields of Representative 3-Aryl-1-(2,6-substituted-3-oxo-pyridazin-5-yl)-2-propen-1-ones



cmpd	R^2	R^6	Y	yield (%)	cmpd	R^2	R^6	Y	yield (%)
B1E1	Me	H	Ph	52	**B3E2**	Ph	H	Ph-4-OMe	60
B1E2	Me	H	Ph-4-OMe	55	**B3E3**	Ph	H	Ph-4-Br	53
B1E3	Me	H	Ph-4-Br	67	**B3E4**	Ph	H	Ph-4-Cl	55
B1E4	Me	H	Ph-4-Cl	55	**B3E5**	Ph	H	Ph-2,4-Cl	50
B1E5	Me	H	Ph-2,4-Cl	50	**B3E6**	Ph	H	Ph-3,4,5-$(OMe)_3$	58
B1E6	Me	H	Ph-3,4,5-$(OMe)_3$	59	**B3E7**	Ph	H	2-Furyl	50
B1E7	Me	H	2-Furyl	60	**B3E8**	Ph	H	2-Thienyl	54
B1E8	Me	H	2-Thienyl	52	**B4E1**	H	Ph	Ph	60
B2E1	Bn	H	Ph	62	**B4E2**	H	Ph	Ph-4-OMe	56
B2E2	Bn	H	Ph-4-OMe	52	**B4E3**	H	Ph	Ph-4-Br	56
B2E3	Bn	H	Ph-4-Br	68	**B4E4**	H	Ph	Ph-4-Cl	50
B2E4	Bn	H	Ph-4-Cl	51	**B4E5**	H	Ph	Ph-2,4-Cl	48
B2E5	Bn	H	Ph-2,4-Cl	52	**B4E6**	H	Ph	Ph-3,4,5-$(OMe)_3$	58
B2E6	Bn	H	Ph-3,4,5-$(OMe)_3$	59	**B4E7**	H	Ph	2-Furyl	57
B2E7	Bn	H	2-Furyl	52	**B4E8**	H	Ph	2-Thienyl	60
B2E8	Bn	H	2-Thienyl	51	**B5E1**	Me	Ph	Ph	58
B3E1	Ph	H	Ph	62	**B6E1**	MOM	Ph	Ph	64

compounds are given in Table 4. Comparison of the activity data for hit compounds (Figure 1) with the data obtained for the novel derivatives prepared in this work (Table 4) demonstrates the improvements that can be achieved in the antiplatelet activity through structural manipulation of model chemotypes. It can be seen that the increase in potency is particularly remarkable on

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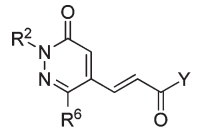
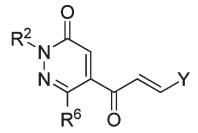
Table 4. Antiplatelet Data Obtained for Representative Pyridazin-3-one/chalcone Hybrids



A1-6D1-8



B1-6E1-8

cmpd	R^2	R^6	Y	IC_{50} (μM)[a]
A4D3	H	Ph	4-Br-Ph	12.27 ± 0.36
A4D5	H	Ph	Ph-2,4-Cl	3.44 ± 0.04
B4E3	H	Ph	4-Br-Ph	9.23 ± 0.84
B4E5	H	Ph	Ph-2,4-Cl	5.51 ± 0.83
A1D4	Me	H	Ph-4-Cl	4.65 ± 0.35
A1D5	Me	H	Ph-2,4-Cl	3.69 ± 0.63
A3D2	Ph	H	Ph-4-OMe	10.97 ± 1.58
A5D3	Ph	H	Ph-4-Br	7.64 ± 0.52
A2D2	Bn	H	Ph-4-OMe	4.94 ± 0.29
A2D7	Bn	H	2-Furyl	11.72 ± 1.11
B1E8	Me	H	2-Thienyl	6.21 ± 2.65
B3E4	Ph	H	Ph-4-Cl	5.56 ± 0.65
B3E5	Ph	H	Ph-2,4-Cl	4.12 ± 1.03
Sulfinpyrazone				509.10 ± 49.00

[a] Mean ± SEM of five separate determinations, IC_{50} value (μM) interpolated from concentration-inhibition curves.

replacing the phenyl group by diverse aryl moieties (**Y**) on the pyridazin-3-one/chalcone hybrids. It is also worth noting that some of the pyridazin-3-ones reported here elicit potent platelet aggregation inhibitory activity, with typical values around 3- to 10-fold higher than those of the starting hit compounds (Figure 1 and Table 4) and markedly higher than that for Sulfinpyrazone. Further studies to complete the pharmacological characterization of the library and to elucidate the structure−activity relationships in these series are currently in progress in our laboratories, and the results will be published elsewhere.

In summary, we have developed a practical and straightforward solution-phase synthesis protocol that enabled the acceleration of the hit to lead process within the framework of a program aimed at the discovery of pyridazinone-based antiplatelet agents. The data highlight the advantages of silica-supported aluminum chloride as an efficient, versatile, and recyclable catalyst for Knoevenagel and Claisen−Schmidt condensations. A full account of the library production, the antiplatelet data, and the main features of the structure−activity relationships in these series will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, spectroscopic data, and copies of NMR and mass spectra for representative compounds are described. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Si-$AlCl_3$ employed in this work was purchased from Sigma-Aldrich. Kimble vials were closed before heating without any pressurization.

Complete description of the spectroscopic, biological and analytical data for representative compounds is included in the Supporting Information.

(19) The platelet aggregation inhibitory activity was examined in vitro on washed human platelets by the turbidimetric method of Born. See: Born, G. V. R. Aggregation of Blood Platelets by Adenosine Diphosphate (ADP) and its Reversal. *Nature* **1962,** *194*, 927–929.