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A Green Chemistry Comparative Analysis of the Syntheses of (*E*)-4-Cyclobutyl-2-[2-(3-nitrophenyl)ethenyl] Thiazole, Ro 24-5904

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Abstract:

The malonic acid, the Wittig−Horner, and Claisen syntheses for the preparation of Ro 24-5904 (1) are analyzed using the Andraos' reaction analysis metrics system. Although this analysis showed the direct coupling of 4-cyclobutyl-2-methylthiazole (19) with 3-nitrobenzaldehyde (5) is the most atom efficient route, the excess of 3-nitrobenzaldehyde (5) required for a reasonable reaction rate at the reported conditions significantly detracts from this chemistry. The malonic acid based synthesis to 3-nitrocinnamide (9) is atom efficient; however the thionation strategy and the use of Lawesson's reagent preclude its consideration. As demonstrated in the elegant Wittig−Horner route, the thionation with hydrogen sulfide is 100%, but the formation of a stoichiometric amount of potassium diethyl phosphate causes the waste mass efficiency to be similar to that for the process with Lawesson's reagent (10). A review of the literature has shown that there is a paucity of general environmentally benign thionating methods and focused R&D activities in a unified approach with different sectors of the chemical industry may serve to alleviate this situation.

Introduction

Route selection is one of the most significant outcomes of process research studies, and during this evaluation, preliminary information about product quality, route efficiency, environmental safety, and process safety can be garnered. Typically, in this effort, a comparative analysis of existing and new chemistry is done in order to highlight deficiencies and to identify future areas of process research and development. This analysis coupled with a thorough review of the scientific literature can also identify the need for development of new synthetic methodology for a particular transformation. With the advent of reaction metrics for environmental analysis, an additional requirement of this effort is also the quantification of the potential environmental impact of a particular route.[1,2]

(*E*)-4-Cyclobutyl-2-[2-(3-nitrophenyl)ethenyl] thiazole, Ro 24-5904 (**1**) is the key intermediate in the synthesis of leukotriene antagonist Ro 24-5913 (**4**) (Scheme 1), and three very different routes have been reported for the preparation of Ro 24-5904 (**1**) (Schemes 2−4).[3−5] The principal synthetic challenges associated with the preparation of Ro 24-5904 (**1**) are the preparation of the thioamide and the stereospecific formation of a trans double bond. These routes do share a common element in that a Hantzsch synthesis is used to construct the thiazole ring, and the raw material used to introduce the 3-aminoaryl group in the final intermediate **2** is the electron-deficient aldehyde, 3-nitrobenzaldehyde (**5**). Raw material costs are also an issue as they relate to the cost of the cyclobutyl group, and as a consequence of this, any transformation when this group is present will be scrutinized with respect to yield and the efficient use of the cyclobutyl-containing entity. This cost might be related to the low yields obtained in the traditional method to synthesize cyclobutyl derivatives by an alkylation of a malonic ester with a dihalide.[6] A different cyclization strategy which utilizes an intramolecular reductive cyclization has been reported, and the relatively inexpensive 2-acetylsuccinate esters are the starting materials for its synthesis.[7]

The patented process to Ro 24-5904 (**1**) utilizes straightforward methodology for the preparation of the trans double bond and standard functional group manipulations to prepare the thioamide **11**. Another advantage of this route is that the costly bromocyclobutylmethyl ketone (**13**) is introduced in the last step of the synthesis of Ro 24-5904 (**1**). Alkylation of the thioamide **11** with bromocyclobutylmethyl ketone (**13**) followed by dehydration completes the synthesis. The principal deficiency in this route is the use of Lawesson's reagent (**10**) as a thionating agent (Scheme 2).[3]

Maehr and others have addressed the issue of the thionating agent by the development of Wittig−Horner chemistry for the construction of the styryl double bond (Scheme 3). Hydrogen sulfide was used as the thionating agent and used to prepare the starting phosphonate **15**. Although this chemistry requires that the cyclobutyl group be introduced at an earlier stage, the yields for both the thiazole construction and the coupling reaction are almost

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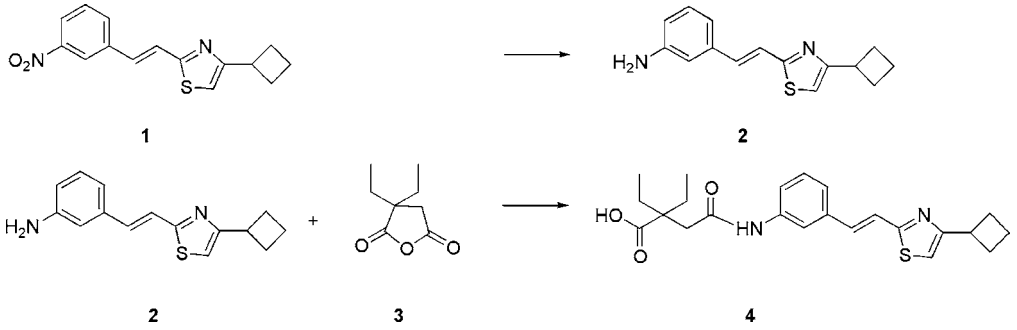
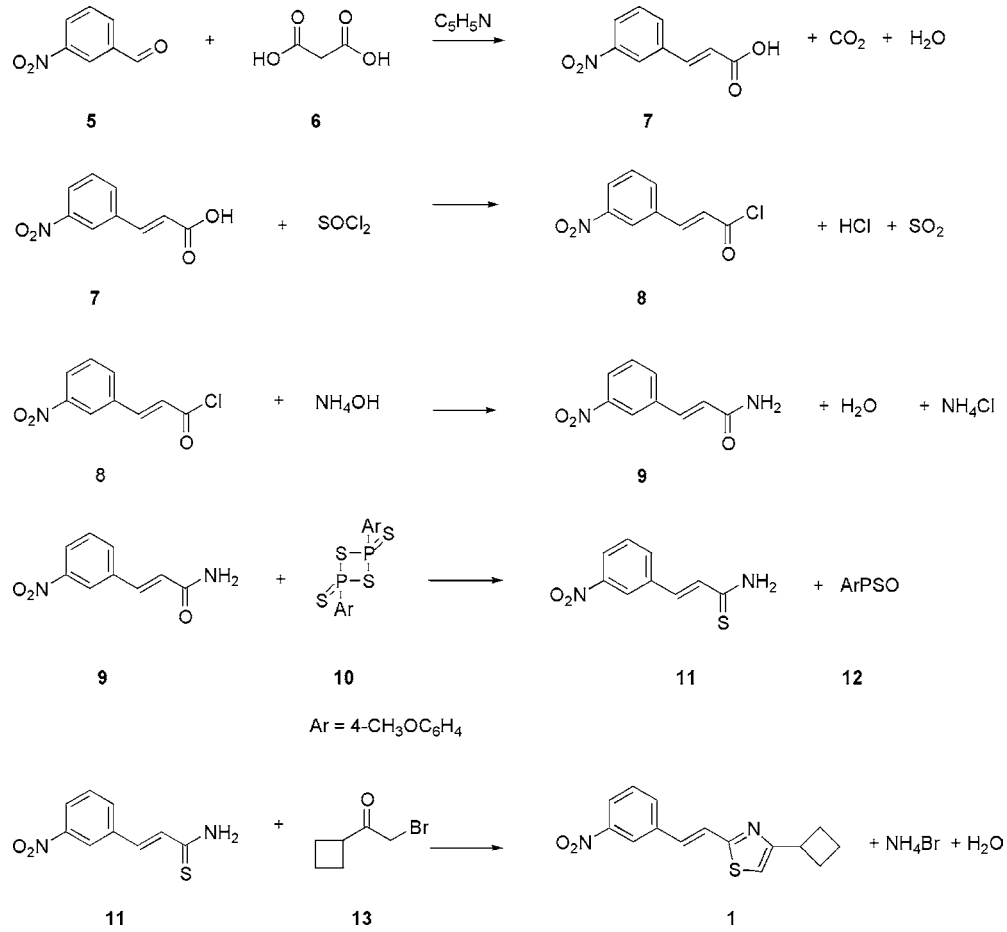
Scheme 1. **Synthesis of Ro 24-5913 (4)**



Scheme 2. **Malonic acid condensation route to Ro 24-5904 (1)**

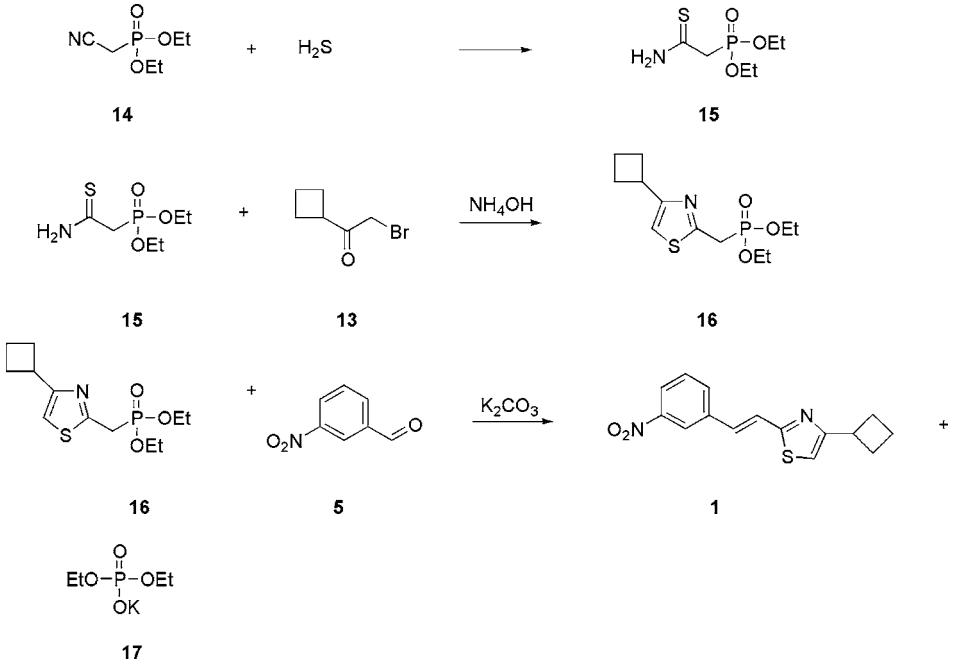


quantitative and an efficient recrystallization procedure was developed to remove the 3% of the contaminating (*Z*)-isomer.[4a] Another distinguishing feature of this chemistry is that the solution combinatorial route to libraries of *N*-aryl-3-(2-thiazolethenyl)anilides is the same route for which preparative quantities of Ro 24-5904 (**1**) could be made.[4b] The routine use of such a strategy may help to foster the development of in-house knowledge for a particular transformation or route.

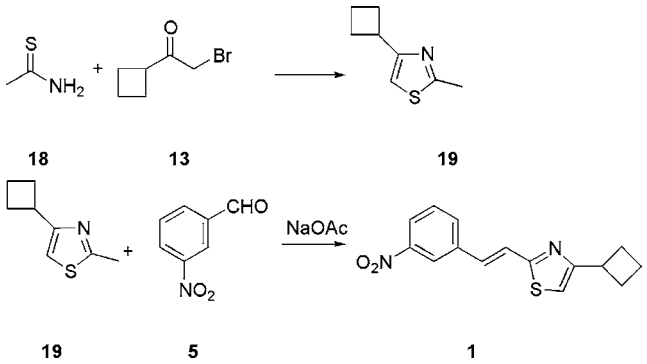
The Wittig−Horner chemistry requires that an activating group be used in order to acidify the C-2 methyl group of the thiazole ring. The patent literature has reported on low yields in the coupling reaction of 4-cyclobutyl-2-methyl-thiazole (**19**) with 3-nitrobenzaldehyde (**5**) (Scheme 4).[3] Mechanistic studies on this reaction indicated that a slow rate for the formation of the carbanion at the C-2 methyl of the thiazole was not the reason for the low yields but rather was due to the more fundamental reason of the lack of reactivity of the 4-cyclobutyl-2-methyl-thiazolium salt with 3-nitrobenzaldehyde (**5**). A large excess of the aldehyde compensated for the lack of reactivity, and the rationale for this was derived by a qualitative assessment of the reaction rate with aromatic aldehydes that contained electron-withdrawing and electron-donating groups.[5]

Andraos has recently reported on a set of unified reaction metrics for the green chemistry analysis of a process.[1] In this work, processes were analyzed for which there was a detailed account of the procedure for the preparation of a final product. This concept has been further elaborated, and a database of reaction metrics for named organic reactions now exists.[2] This green chemistry metrics analysis has now

Scheme 3. **Wittig−Horner route to Ro 24-5904 (1)**



Scheme 4. **Claisen condensation route to Ro 24-5904 (1)**



also been extended to include an analysis of energy usage.[8] Because detailed process information would not be available during the earlier stages of process research and development, we wish to report on a comparative analysis of the aforementioned routes for the synthesis of Ro 24-5904 (**1**). This analysis is important as it can highlight environmental issues at an earlier stage in development and, more importantly, can identify the need for fundamental research in the development of new synthetic methodology or in the reclaimation of byproducts.

Despite the fact that the thiazole ring is present in commercially significant materials such as vitamin B_1,[9] thionating methodology was not included in a survey of named organic reactions.[2] Thioamides can also be useful synthetic intermediates as demonstrated in the patented process for the synthesis of HIV-1 reverse transciptase inhibitor Emivirine.[10] Hydrogen sulfide, which is either used as a reagent or is produced as a byproduct, is a poisonous, flammable noxious substance.[11] The organoleptic detection threshold limit for hydrogen sulfide is 6.4×10^{-10} mol/dm^3.[12] Hydrogen sulfide is acutely toxic with an LC_{50} of 444 ppm in rats over a 4 h period.[13] As a result of a release of 900 pounds of hydrogen sulfide at a gas refinery in the Virgin Islands, the details of the chronic effects of exposure of hydrogen sulfide have also been reported.[14] These characteristics of hydrogen sulfide further make the early environmental evaluation of a route which will utilize hydrogen sulfide, generate hydrogen sulfide, or involve potentially moisture-sensitive intermediates such as thioamides important.

Results and Discussion

The reported literature procedures for these three different processes, the malonic acid synthesis, the Wittig−Horner route, and the Claisen condensation, have been developed to different extents. For these processes, the E_{mw} (the environmental factor based on molecular weight), AE (atom economy), RME (reaction mass efficiency), SF (stoichiometric factor), and the E_m (the environmental impact factor based on mass) were calculated using the procedures that were reported in the literature. None of these processes utilize extreme conditions of temperature and pressure. All of these processes either utilize hydrogen sulfide or involve the synthesis or use of compounds that can liberate hydrogen sulfide such as thioamides. Up until the point in the process when the thioamide is transformed to a thiazole, these

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Table 1. **E_m for the preparation of Ro 24-5904 (1)**

overall yield	100%	literature	literature	100%
excess reagents	none	none	literature	literature
		Route		
malonic acid	1.673	2.394	3.416	2.480
Wittig−Horner	1.614	1.920	3.190	2.800
Claisen	0.657	1.239	2.791	1.805

thioamide intermediates are capable of producing hydrogen sulfide. Process development on any of these routes will involve studies on process efficiency, capacity improvements, and waste minimization. However, if a route is transferred to development in which there is inherently a significant amount of generated waste, development studies can only make incremental changes in the amount of waste that is produced. Parallel process research studies may identify a route in which a fundamental reduction in the amount of waste can be achieved.

The importance of the Andraos analysis is that it characterizes waste only on a mass basis. Although, in many instances, methodology to recover the waste and to either reclaim it or recycle it may be developed, such scenarios may not be implemented in practice and may not be done during the clinical development of a new pharmaceutical. These practices could contribute to the reason that the pharmaceutical industry produces the most waste on a weight ratio basis.[15] In these three routes, the molecular characteristics of the inherent waste streams are dramatically different, and this characteristic may ultimately lead to a selection of a particular route.

At a 100% yield and with no excesses of reagents, this analysis shows that despite the use of Lawesson's reagent (**10**) and because of its relative simplicity, the malonic acid process as compared to the elegant Wittig−Horner route has a comparable E_{mw}. When a thioamide is synthesized from an amide, 0.5 equiv of Lawesson's reagent (**10**) is used and only two of the sulfur atoms are available. When a thioamide is synthesized from a nitrile and hydrogen sulfide is the reagent as in the Wittig−Horner route, 1 equiv of hydrogen sulfide is required. In the Claisen route, the thioamide is purchased as the readily available thioacetamide (**18**) and the environmental impact factor based on molecular weight (E_{mw}) is 61% less than that for the malonic acid route. At the conditions when there are no excesses of reagents and the yields are 100%, the E_{mw} is equal to the E_m. Because there is an inverse relationship between E_{mw} and AE, the atom economy for the Claisen condensation is the highest as the only byproducts are water and ammonium bromide (Table 1).

In practice, the low reactivity of the thiazole **19** towards 3-nitrobenzaldehyde (**5**) required that 3 mol of the aldehyde **5** be used, and this process characteristic would not be gleaned from a comparative analysis of E_{mw}. Because reasonable literature procedures are available for all of these routes, the next level of analysis is to calculate the E_m at the actual yield and the described excesses. For the malonic acid route, a related example in the Roche patent was used for the yield and an equivalent amount of Lawesson's reagent (**10**) for the conversion of amide **9** to thioamide **11**.[2] For the preparation of *m*-nitrocinnamic acid (**7**), a literature procedure was evaluated and *Organic Synthesis* procedures for the conversion of an acid to an acid chloride[16] and an acid chloride to an amide[17] were used in the calculations. The quantitative conversion for the Hantzsch thiazole synthesis of thiazole **16** by the use of a slight excess of bromomethyl cyclobutyl ketone (**13**) was used for the synthesis of Ro 24-5904 (**1**) in the malonic acid route and for the formation of the respective thiazoles **16** and **19** by the Wittig−Horner and the Claisen routes (Table 2).

Table 2. **Detailed route reaction metrics analysis for the preparation of Ro 24-5904 (1) at the reported conditions**

route	yield	E_{mw}	AE	RME	E_m
malonic acid	65.6%	1.673	0.374	0.226	3.416
Wittig−Horner	79.9%	1.614	0.382	0.239	3.190
Claisen	74.0%	0.657	0.604	0.264	2.791

For a more detailed route analysis of the Wittig−Horner chemistry and the Claisen condensation, only the excesses of reagents were considered and solvent use was excluded. This analysis shows that the Wittig−Horner chemistry would produce 3.190 kg of waste/kg of product and that the Claisen route would produce 2.791 kg of waste/kg of product. Presumably, the 3-nitrobenzaldehyde (**5**) could be recovered by either extraction with sodium bisulfite or conversion of Ro 24−5904 (**1**) to its hydrochloride salt and recycling of the mother liquors. This chemistry does produce tar, and so polymeric byproducts may accumulate in the process stream if the mother liquors were recycled. A reduction in the amount of tar to facilitate the recovery of 3-nitrobenzaldehyde (**5**) and product separation and isolation could be an area of future process development activities.

The excess of aldehyde **5** was used to compensate for the poor reactivity, and in the patented procedure, equimolar amounts of the aldehyde **5** and thiazole **19** were used. Pagnai has reported on the condensation of bisthiazolyl methane with an aldehyde in the presence of acetic acid and acetic anhydride.[18] In this example, the presence of an additional acidifying group necessitated the use of only a stoichiometric amount of the aldehyde. If such a process would be operative in the present example, then a Knoevenagel condensation of ethyl (4-cyclobutyl-2-thiazolyl)acetate (**22**) with 3-nitrobenzaldehyde (**5**) may yield the stryrl thiazole (**23**) in which only a molar amount of aldehyde **5** was used. Saponification and decarboxylation would afford Ro 24-5904 (**1**). Analysis of this hypothetical route shows that at 100% yield and stoichiometric amounts of reagents, an E_m of 1.112 kg of waste/kg of Ro 24-5904 (**1**) would be obtained (Scheme 5).

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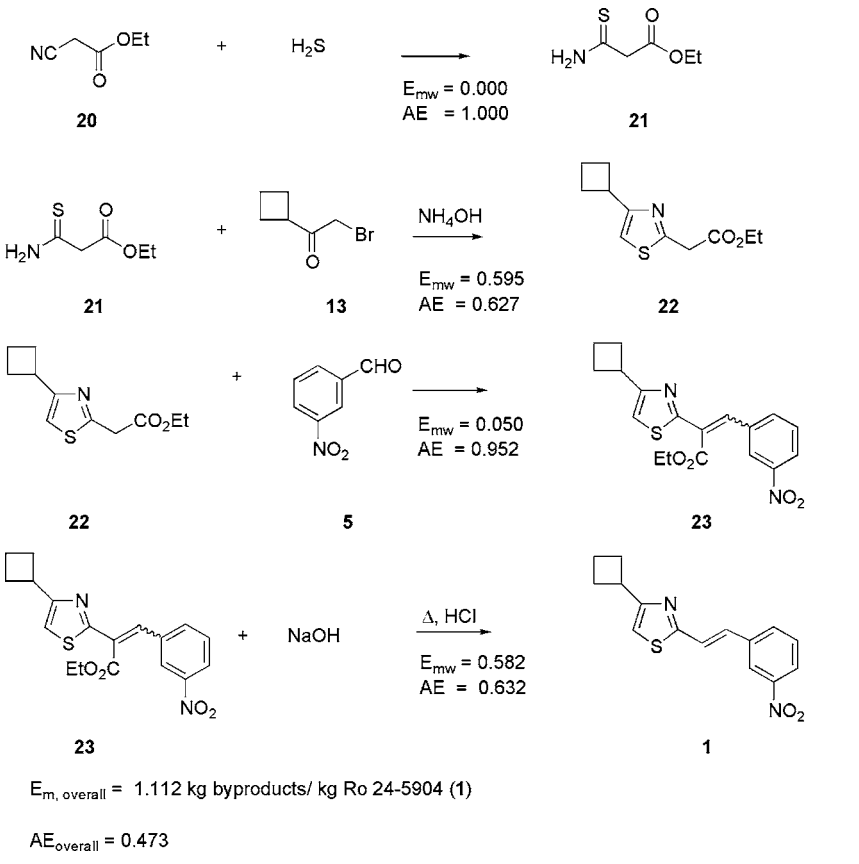
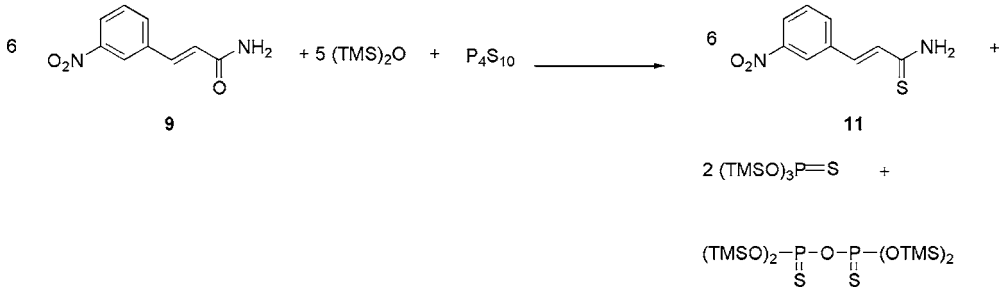
Scheme 5. **Hypothetical modified Claisen route to Ro 24-5904 (1)**



$E_{m,\ overall}$ = 1.112 kg byproducts/ kg Ro 24-5904 (**1**)

$AE_{overall}$ = 0.473

Scheme 6. **Synthesis of thioamide 11 using Curphey's method**



If an average yield of 90% for the four steps for the preparation of thioamide **11** could be achieved by process development studies with no reagent excesses, then a decrease of route E_m to 2.394 kg of waste/kg of Ro 24-5904 (**1**) could be obtained. This value is still inherently 17% higher than that for the Wittig−Horner process with no real possibility of lowering it by further process development studies. Reduction in the mass of waste product can only be achieved by the use of a different thionating agent.

The need for the development of better thionating agents in particular of amides to thioamides is evident in the literature, as there have been several reports in which new reagents have been developed. The combination of a phosphorus pentasulfide and hexamethyldisiloxane can thionate a variety of different functional groups including amides into their corresponding thiono derivatives.[19] The thioamide **11** is produced directly by this chemistry, and although the byproducts of this thionation reaction can readily be removed by methodology other than chromatography, the E_m for the combination of phosphorus pentasulfide and hexamethyldisiloxane is larger than the E_m when Lawesson's reagent (**10**) is used (Scheme 6). A process which would utilize the noxious, difficult to handle phosphorus pentasulfide has an E_m comparable to that for Lawesson's reagent (Table 3).[20]

The shortcoming of the malonic acid synthesis is that an adequate way to prepare the thioamide (**11**) from the amide (**9**) has not been demonstrated. The formation of 3-nitrocinnamide (**9**) from 3-nitrobenzaldehyde (**5**) is a process, which can be engineered, and in these studies, the most appropriate reagent for the formation of the acid chloride can be identified. To a great extent, the choice of the chlorinating agent such as either thionyl chloride or oxalyl chloride will internally depend on the facility and the ability to handle

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Table 3. **Reaction metrics for thionating reagents**[a]

thionating reagent	byproducts (molecular weights)	stoichiometry	E_{mw}	AE	RME	E_m
Lawesson's reagent	186.17	0.500	1.673	0.374	0.295	2.394
Curphey's reagent	661.20	0.333	2.406	0.294	0.238	3.209
	495.73	0.167				
phosphorus pentasulfide	507.88	0.167	1.644	0.378	0.297	2.362

[a] Calculations on SF = 1 for the route and an overall yield of 65.6%.

these reagents and their associated byproducts of hydrogen chloride and either carbon monoxide or sulfur dioxide. Within this context, a reaction to produce 3-nitrocinnamide (**9**) directly from 3-nitrobenzaldehyde (**5**) was reported many years ago by the condensation of 3-nitrobenzaldehyde (**5**) with diacetamide. The formation of 3-nitrocinnamide (**9**) was confirmed, and a Perkin-like mechanism was claimed by the authors.[21]

Although the driving force for thionation with Lawesson's reagent (**10**) is understood, the byproduct **12** from the Lawesson reaction has not been defined and methodology to regenerate the reagent has not been developed.[22,23] Phosphorus pentasulfide is the traditional reagent for the thionation of carbonyl groups, and phosphorus pentasulfide in combination with an amine can afford a thioamide directly from a carboxylic acid.[24]

Various sulfur reagents other than those associated with pentavalent phosphorus have recently been reported. In a conventional reactor, the use of triflic anhydride, pyridine, and ammonium sulfide to prepare secondary and tertiary thioamides has been described. In this work, the amide is activated by the formation of the pyridium salt. Nucleophilic addition of sulfide to this activated amide affords the thioamide. The absence of any primary thioamides as reported examples is conspicuous.[25]

A report has recently appeared that sodium hydrogen sulfide and magnesium chloride in dimethyl formamide affords primary thioamides in yields of 80−99%.[26] Bagley and others have reported on a microwave-assisted synthesis of primary thioamides using ammonium sulfide from nitriles. For the example when the reactant was 2-cyanopryridine, the thionation reaction was quantitative either in solution at room temperature or with microwaves. Sodium hydrosulfide was ineffective in this conversion. Acetonitrile could be converted into thiaocetamide at room temperature, but only a 53% yield could be obtained with microwave irradiation. The beneficial effect of microwaves may be that the byproduct, ammonia, can be removed from the reaction and reactions to form amidines are precluded. When acrylonitrile was subject to these reaction conditions, only the conjugate addition product was obtained.[27] By careful pH control, a thioamide can be prepared from a nitrile and the sulfuration reagents can include ammonium sulfide and sodium hydrogen sulfide. Such a process has been patented by Bayer.[28] For the use of these thionating agents, a Knoevenagel condensation of cyanoacetate ester with 3-nitrobenzaldehyde (**5**) would be perhaps a more suitable alternative to prepare the (*E*)-3-nitrocinnamonitrile.[29] A report on this condensation in an ionic liquid and a related condensation[30] has also appeared.[29a]

What Would Make These Routes Green? The Wittig−Horner process affords the target product in high yield and purity, and process control[31a] of the formation of the (*Z*)-isomer in the final product has been accomplished by a selective recrystallization process.[31b] Although diethoxyphosphinyl thioamide is commercially available,[32] the known route to produce the thioamide **15** is atom efficient and this step in the process is inherently green, whether the process is conducted in-house or outsourced. The drawback in this chemistry is the stoichiometric amount of potassium diethyl phosphate (**17**) that is produced in this process. As with the case of the byproduct of the Wittig reaction, triphenylphosphine oxide,[33] a way to reclaim byproduct **17** would be necessary. Because this product **17** is likely to be a fertilizer in an aquatic environment, the development of methodology to reclaim it should be done in tandem with route development. On a weight ratio basis, this elegant process produces approximately the same amount of waste as the malonic acid condensation.

In the balanced chemical equation for the Claisen condensation, 1 mol of 3-nitrobenzaldehyde (**5**) is used. In practice and because of the poor reactivity, a large excess of the aldehyde **5** was required. Aldehyde **5** could presumably be recovered by the formation of the bisulfite adduct. However, the fundamental problem in this chemistry is the low reactivity of the salt of thiazole **19**. With the advent of the development of ionic liquids as commercial solvents, the rate enhancements seen in these solvents could very well facilitate the rate of this condensation. These rate enhancements have been observed in similar reactions such as a Claisen rearrangement.[34] The condensation of equimolar

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amounts of 4-dimethylaminobenzaldehyde with 2-methylbenzothiazole in hydrochloric acid at 100 °C for 16 h yielded the related stryrl benzothiazole in a 76% yield.[35] An iron reduction has been used successfully to prepare 2,4-diaminobenzaldehyde from 2,4-dintrobenzaldehyde,[36] and scale-up issues for iron reduction in acetic acid have been evaluated by the Drug Evaluation Department at Johnson & Johnson.[37] The analogous preparation with the hydrochloric salt of 3-aminobenzaldyde would eliminate another step with the costly cyclobutyl group and also any issues with overreduction of the double bond in Ro 24-5904 (**1**). The electron-withdrawing effect of the protonated amine would accelerate the reaction rate and, thus, reduce the excess amount of the aldehyde.

Conclusion

At the stage of the balanced chemical equation and using literature procedures, both the atom economy and the waste mass efficiency of three different routes to a key stryrl thiazole intermediate (**1**) were calculated. This analysis served to highlight the deficiencies in these routes and to identify areas of future green chemistry process research and development studies. Although it was expected that fundamental changes in the route will perhaps have the greatest impact on the kind of waste that is produced, this analysis also shows that process research can also make core reductions in the amount of process waste. A further striking outcome of this analysis is that the elegant Wittig−Horner route would produce approximately the same amount of waste as the route which uses Lawesson's reagent (**10**). Although a large excess of aldehyde **5** is used in the Claisen synthesis, this route produces the least amount of waste.

The industry gold standard for a pharmaceuticals process in which solvent usage and recycling scenarios are considered would be the Viagra (sildenfal) process. The calculated overall environmental impact factor based on mass, E_m, is 5.96 kg of waste product per kg of sildenfal. The details of this manufacturing process have been disclosed, and importantly, significant development efforts were undertaken to set this benchmark for the pharmaceutical industry.[38] Industry-wide standards for the use of these metrics could be perhaps future requirements for the CMC (Chemistry, Manufacturing, Control) section of an NDA or an ANDA.

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Supporting Information Available

The balanced chemical equations and spreadsheet information for the calculation of E_{mw}, AE, SF, RME, and E_m for the routes described in Schemes 2−4. This information is available free of charge via the Internet at http://pubs.acs.org.

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