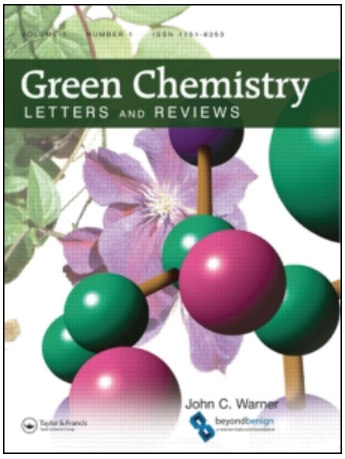


Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Achieving synthetic efficiency through new method development

Jinhua J. Song[a]; Jonathan T. Reeves[a]; Daniel R. Fandrick[a]; Zhulin Tan[a]; Nathan K. Yee[a]; Chris H. Senanayake[a]
[a] Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA

To cite this Article Song, Jinhua J. , Reeves, Jonathan T. , Fandrick, Daniel R. , Tan, Zhulin , Yee, Nathan K. and Senanayake, Chris H.(2008) 'Achieving synthetic efficiency through new method development', Green Chemistry Letters and Reviews, 1: 3, 141 — 148
To link to this Article: DOI: 10.1080/17518250802592360
URL: http://dx.doi.org/10.1080/17518250802592360

Green Chemistry Letters and Reviews
Vol. 1, No. 3, September 2008, 141–148

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Achieving synthetic efficiency through new method development†

Jinhua J. Song*, Jonathan T. Reeves, Daniel R. Fandrick, Zhulin Tan, Nathan K. Yee and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA

(Received 17 October 2008; final version received 31 October 2008)

In this review article, we present an in-depth analysis of three projects from our recent programs to highlight the green chemistry commitment and accomplishments at Boehringer Ingelheim Pharmaceuticals. In all three cases, dramatic reductions in E-factors were achieved, mainly by shortening the synthetic routes and by implementing newly developed synthetic methodologies.

Keywords: E-factors; green chemistry; process chemistry; new methods

Introduction

R&D Process is a very complex undertaking which involves multiple disciplines including process chemistry, reaction safety, solid state characterization, chemical engineering and analytical chemistry (Figure 1). The objective of this multi-disciplinary exercise is to produce Active Pharmaceutical Ingredients (APIs) at the lowest cost with the least amount of wastes generated in the process. Therefore, the "Green Chemistry Initiative" pioneered by Anastas and Warner (*1*) has naturally become an integral part of our research and business strategies in R&D process.

The synergy between green chemistry and process chemistry (in the traditional sense) is shown in Table 1. Syntheses having characteristics listed in the column 1 not only offer high efficiencies from a synthetic chemistry point of view (column 2), but they also use less energy to run and generate much less wastes (column 3), leading to environmentally more friendly processes. For example, if we could cut down the number of synthetic steps by half, then we could immediately reduce the production cost, production time and solvent usage by at least 50%, if not more. Or if we could replace a chemical resolution step with a practical asymmetric method, we could avoid sending half of the valuable materials to the waste drums. Therefore, we believe that chemistry innovation is critical for achieving practical and environmentally sound processes, and it should receive top attentions throughout the API development cycle.

The greenness of a process can be measured by using a number of metrics. The one that is often used is the E-factor which was introduced by Sheldon more than 15 years ago (*2*). It is defined as the total amount of wastes generated for producing 1 kg of product. Within Boehringer Ingelheim (BI), when we calculate E-factors, we include all the water used in the process and all outsourced steps. We assume no recycling of solvents at the early stage of a project. So when we compare different E-factors, there will be a certain degree of consistency across the board within BI. But even so, it is important to keep in mind that there are many other factors that are not included in E-factors. For example, E-factors do not include steps for making commonly available raw materials (e.g., *n*-BuLi) and do not take into account the production volume or the nature of the wastes. But overall, E-factors are a very good indicator of the greenness of a chemical process. In the following sections, three case studies will be presented to highlight the power of process research in improving synthetic efficiencies and reducing E-factors.

Efficient synthesis of 6-azaindoles

One of our drug candidates contains a 6-azaindole subunit (**1**, Scheme 1). The black dot represents a molecular weight of about 300 g/mol with multiple functionalities.

The original medicinal chemistry synthesis was based on Larock's indole synthesis (*3*). Alkyne **4** was

*Corresponding author. Email: jeff.song@boehringer-ingelheim.com
†This paper was presented at the 2nd International Symposium on Green Processing in the Pharmaceutical and Fine Chemical Industries, held at Yale University, May 29–30, 2008.

ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518250802592360
http://www.informaworld.com

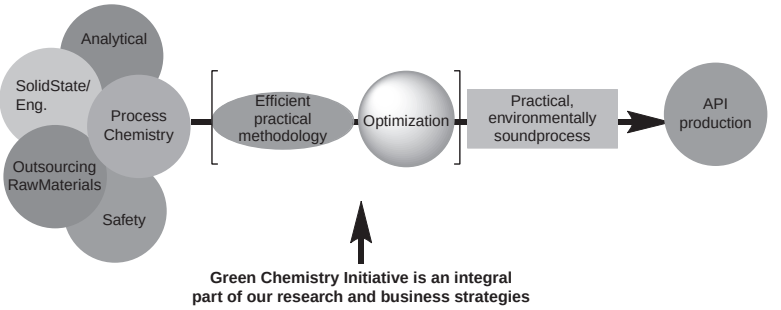
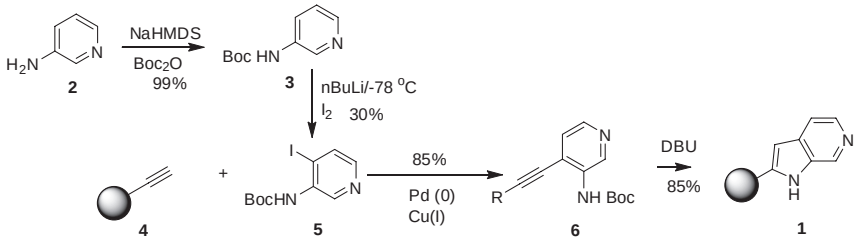


Figure 1. Green chemistry in process R&D.

Table 1. Synergy between process chemistry and green chemistry.

	Process chemistry consideration	Environmental consideration
Use a minimal number of synthetic steps	Efficiency	Less energy and wastes
Develop easy isolation, no SiO_2	Scalability, throughput	Less wastes (solvents)
Avoid cryogenic conditions	Scalability, robust, lower cost	Less energy
Achieve high selectivity (chemo, stereo and regio)	Efficiency/easy purification	Less wastes
Avoid hazardous reagents and reactions	Safety, scalability	Safety, less pollution
Use inexpensive, available raw materials	Cost, lead time	Know-how for waste management
Minimize oxidation state adjustments	Efficiency	Less wastes, potential pollution (metals)
Minimize the use of protecting groups	Efficiency, atom economy	Less wastes



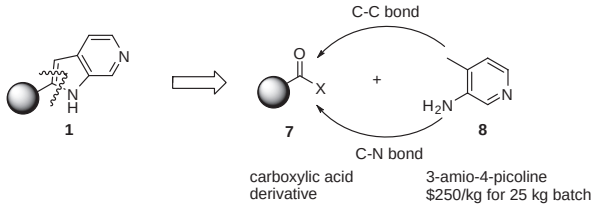
Scheme 1.

coupled with iodopyridine **5**, which was synthesized from 3-aminopyridine in two steps in low yields. Isolation of compound **5** required a labor-intensive chromatography. Then DBU (1,8-diazabicycloundec-7-ene)-mediated cyclization gave the 6-azaindole product (*4*). This synthesis had four steps in total. The E-factor was 364 kg/kg and the cycle time was at least five weeks on Kilolab scales.

In our new retrosynthetic analysis, we disconnected two adjacent covalent bonds as indicated in Scheme 2 to give back two simple building blocks: a carboxylic acid derivative **7** and the readily available 3-amino-4-picoline (**8**). Our proposed reaction sequence would involve the initial formation of the C–C bond followed by cyclization and dehydration to give the target compound. To enable this transformation, a dianion derived from the unprotected 3-amino-4-picoline would be required (reactive intermediate **9**, Scheme 3) (*5*).

We started our experiments by investigating the dilithiation of 3-amino-4-picoline with several strong bases (*6*). The degree of dilithiation was determined by deuterium labeling at the methyl position. With *t*-BuLi at 0°C, 40% of dilithiation was obtained. However, significant side reaction between *t*-BuLi and pyridine ring occurred at this temperature. Treatment of 3-amino-4-picoline with 3 eq of *n*-BuLi at room temperature led to only 25% dilithiation. The Schlosser base, on the other hand, behaved similarly to *t*-BuLi. Finally, we were delighted to find that when 3-amino-4-picoline was treated with 3 eq of *s*-BuLi at room temperature, 70% dilithiation was attained after 3 h.

After the dianion was formed, the reaction mixture was cooled back to -30°C. Ethyl benzoate was then added into the reaction vessel. After the aqueous workup, 2-phenyl-6-azaindole was isolated in 88% yield in a single step. This new methodology



Scheme 2.

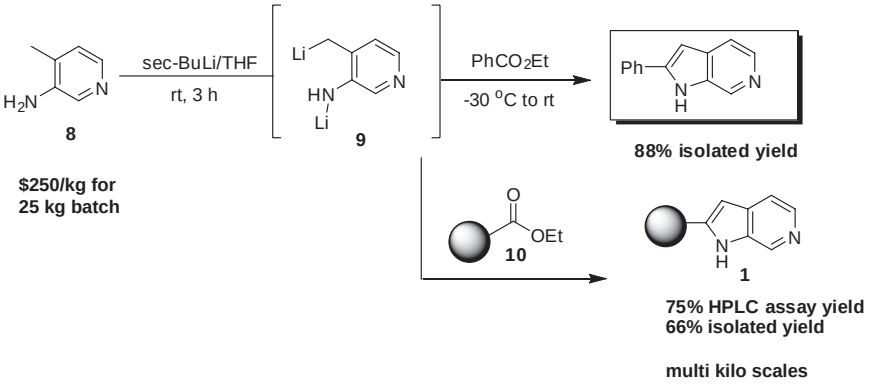
compares favorably with those methods known in the art. For example, to make the same compound (2-phenyl-6-azaindole), it would take three to four steps using literature protocols in modest yields (40–50%) (*7*).

This one-step method was successfully applied to our complex substrate **10** to give 75% assay yield and 66% isolated yield of compound **1** on large scales. The E-factor was thus reduced from 364 kg/kg to only 45 kg/kg (Table 2). This dramatic drop in E-factor is mainly attributed to the brevity of the new route. By going from four steps to only one step, we cut out >80% of the wastes. Furthermore, the new route does not use cryogenic conditions or heavy metals. The cycle time now is only one week, thereby saving substantial amounts of energy and resources in the plant.

Selective formation of 5-bromo-2-pyridyl magnesium chloride

The next project involves the synthesis of 5-bromo-2-pyridyl aldehyde (**14**, Scheme 4). The original synthesis started out with 2,5-dibromopyridine. The Pd-catalyzed carbonylation (*8*) gave monoester **13** which was reduced by DIBAL (diisobutylaluminum hydride) at −78°C to give aldehyde product **14**.

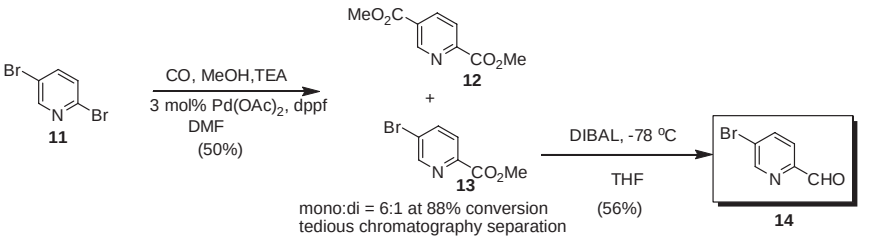
However, this simple-looking two-step sequence had some very serious scaleup issues. The major problem with the carbonylation reaction is that once



Scheme 3.

Table 2. Comparison of old and new routes.

	Old route	New route	Environmental consideration
E-factor	364 kg/kg	45 kg/kg	80% less wastes
Number of synthetic steps	4	1	Less energy and wastes
Cryogenic conditions	−78°C	None	Less energy
Selectivity	Ortho-Li	No issue	Less wastes
Silica	1	None	Less wastes (solvents)
Special material handling	*n*-BuLi	*s*-BuLi	Safety
Heavy metals	Pd and Cu	None	Less wastes
Oxidation state adjustments	1	None	Less wastes
Protecting groups	1	None	Less wastes
Cycle time	Five weeks	<One week	Less time/manpower/energy



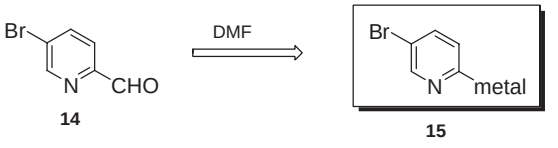
Scheme 4.

the desired monoester **13** is formed, it can further react under the reaction conditions to give diester **12** as a by-product. This side reaction is so competitive that even at low conversions, a significant amount of diester is formed in the reaction mixture. For example, at 88% conversion, close to 15% diester was formed. The separation of the monoester and diester required tedious chromatography. As a consequence, the process had a high E-factor of 305 kg/kg with a five-week cycle time on Kilolab scales.

In our new retro-synthetic analysis (Scheme 5), we envisioned that if an anion could be generated at the C(2) position of the pyridine ring in the presence of the C(5) bromine (such as in **15**), then quenching this anion with DMF (dimethylformamide) should give aldehyde **14** in one step. This approach would allow us to completely bypass the inefficient carbonylation reaction as well as the DIBAL reduction, thereby increasing the overall efficiency.

Back in 1999 when we started the work, a literature survey revealed that, for 2,5-dibromopyridine, metal-halogen exchange reactions actually happen at C(5) position (Scheme 6). It was reported that treatment of 2,5-dibromopyridine with *n*-BuLi or *i*-PrMgCl gave five-metallated products with high selectivities (*9*). It is apparent that the C(5) position of the pyridine ring is intrinsically favored in metal-halogen exchange reactions.

In order to overweigh the intrinsic electronic bias for the C(5) position of the pyridine ring, we decided to employ a pyridine starting material with two differential halogens, e.g., 5-bromo-2-iodopyridine (**16**, Scheme 7).[1] When 5-bromo-2-iodopyridine was treated with *n*-BuLi in THF (tetrahydrofuran) at $-78^{\circ}C$, lithiation occurred instantly to afford 5-bromo-2-lithiopyridine. However, the lithiated pyridine started to decompose in a short period of time, especially at a temperature higher than $-50^{\circ}C$.



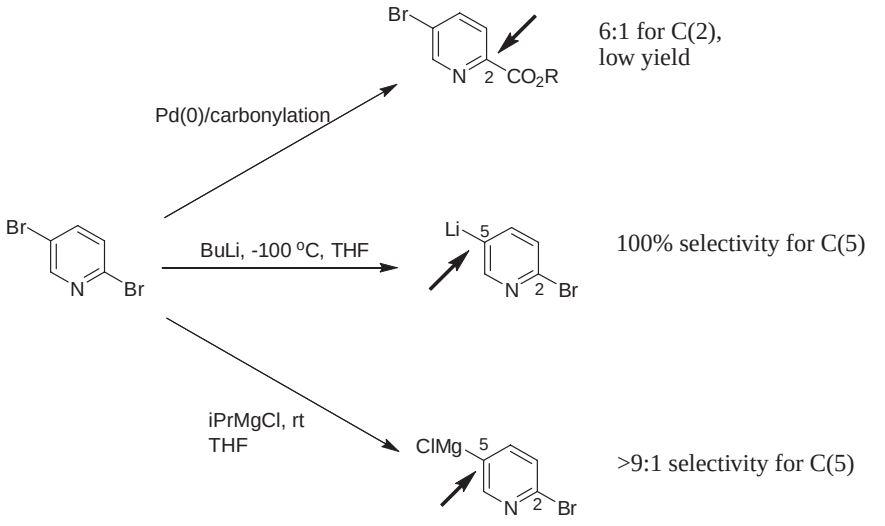
Scheme 5.

To overcome the stability issue associated with lithiopyridines, we turned our attention to magnesium-halogen exchange reactions (*11*). When a THF solution of 5-bromo-2-iodopyridine was treated with *i*-PrMgCl at $0^{\circ}C$, a slurry was formed within 30 min. Upon quenching with MeOH-d_4, 3-bromopyridine was isolated with $>95\%$ D incorporation at the position para to bromine, which was consistent with the formation of the desired Grignard intermediate (**17**). Treatment of the Grignard intermediate with DMF gave, after aqueous workup, aldehyde **14** in 87% isolated yield. This reaction has been scaled up to 40 kg batches without any problems.

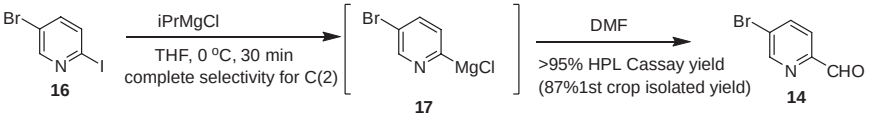
After we have completed our study on the Grignard chemistry, some very nice work was published from two other research groups on the C(2)-selective lithiation of 2,5-dibromopyridines (*12*). It was reported that the unstable 5-bromo-2-lithiopyridine could be stabilized by either employing the high dilution/low temperature conditions (e.g., ~ 0.085 M, $-50^{\circ}C$, Wang et al.) or by using 2-*N*,*N*-dimethylaminoethanol (Gros et al.). Unfortunately, although these methods significantly slow down the decomposition of the lithiopyridine, the C(2)/C(5) selectivity still slowly erode over time. In contrast, by using 5-bromo-2-iodopyridine, a very stable C(2)-pyridyl Grignard can be formed with complete selectivity at $0^{\circ}C$ in 0.5 M reaction concentration. The Grignard chemistry allowed us to reduce the E-factor from 305 kg/kg to 32 kg/kg (90% reduction in wastes, Table 3). The new route does not require cryogenic conditions, silica columns, oxidation state adjustment or the use of heavy metals.

One-step conversion of carboxylic acids into trifluoromethyl ketones

The final project for this article is the synthesis of a trifluoromethyl ketone (**22**, X is a halogen, Scheme 8). Compound **22** was initially prepared using a four-step sequence with ethyl trifluoropyruvate as the starting material (*13*). Addition of the methallyl Grignard



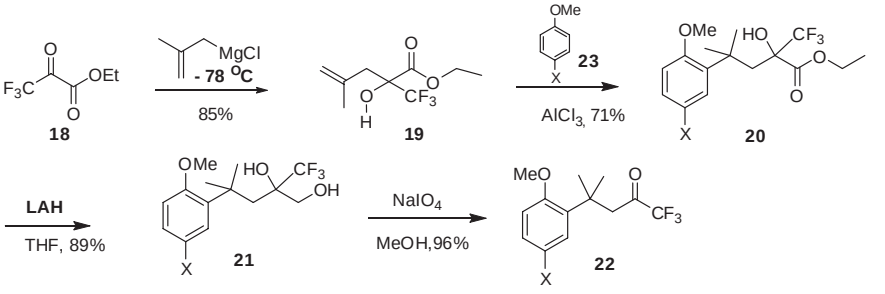
Scheme 6.



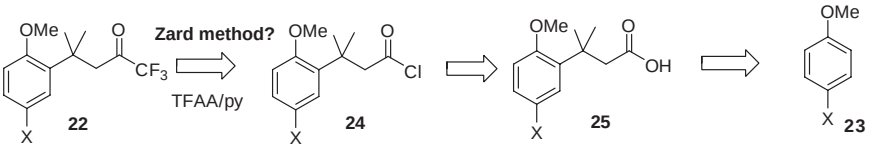
Scheme 7.

Table 3. Comparison of old and new routes.

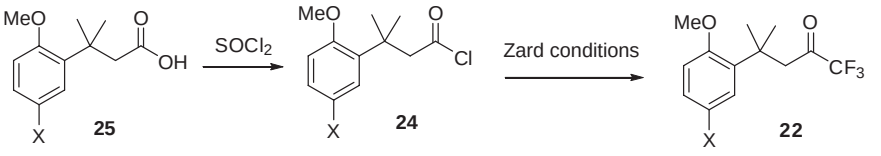
	Old route	New route	Environmental consideration
E-factor	305 kg/kg	32 kg/kg	90% less wastes
Number of synthetic steps	2	1	Less energy and wastes
Cryogenic conditions	−78°C	None	Less energy
Selectivity	6:1	100%	Less wastes
Silica	1	None	Less wastes (solvents)
Reagent handling	DIBAL, CO	*i*-PrMgCl	Safety, less pollution
Heavy metal	3 mol%Pd	None	Less wastes
Oxidation state adjustment	1	None	Less wastes
Cycle time	Four weeks	One week	Less time/manpower/energy



Scheme 8.



Scheme 9.



reagents	T	reaction time	results
TFAA, pyr. CH_2Cl_2,	22 °C	--	no reaction
TFAA, pyr. CH_2Cl_2,	40 °C	4 days	60%

Scheme 10.

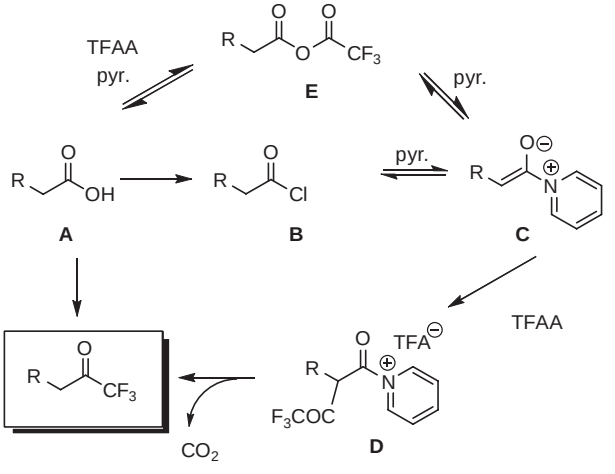
reagent at $-78°C$ gave racemic tertiary alcohol **19** in good yield. The left-hand side was attached through an $AlCl_3$-catalyzed Friedel-Crafts alkylation reaction. The ester was then reduced to the alcohol by lithium aluminum hydride. The resulting diol **21** was oxidatively cleaved to give the trifluoromethyl ketone **22**. The E-factor was 135 kg/kg.

Our new retrosynthetic analysis (Scheme 9) was inspired by a very unique method reported by Zard and co-workers who have found that certain carboxylic acid chlorides could be converted into the corresponding CF_3 ketones using TFAA (trifluoroacetic anhydride) and pyridine in CH_2Cl_2 at room temperature (*14*).

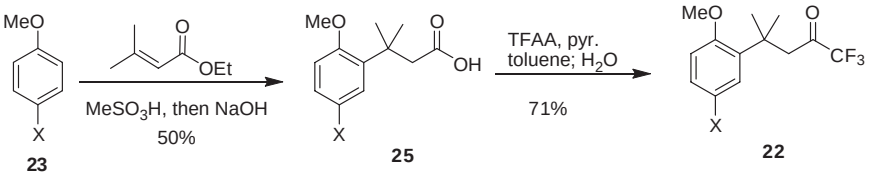
This method proved to be useful for our substrate. Treatment of acid **25** with oxalyl chloride gave acid chloride **24**, which was then taken into the TFAA/pyridine step (Scheme 10). At reflux (40°C) the reaction proceeded slowly, requiring ~4 days for completion, but nonetheless providing ketone **22** in 60% yield. However, the reaction was too slow to be practical on scale. Furthermore, the synthesis used methylene chloride as the reaction solvent and required two synthetic steps.

In order to improve this transformation, we took a closer look at the reaction mechanism (Scheme 11). Zard and co-workers proposed that acid chloride B is first converted into intermediate C which can be considered a ketene equivalent. Subsequent acylation by TFAA gives compound D which will decarboxylate upon treatment with water to furnish the trifluoromethyl ketone. It occurred to us that we may be able to access the key intermediate C directly from the acid by treatment with TFAA. Initial reaction of acid A with TFAA should form a mixed anhydride E which should react further in the presence of pyridine to give intermediate C. If this works, we could streamline this transformation into a one-step operation.

Indeed, it was found that heating acid **25** in toluene at 65°C in the presence of TFAA and pyridine gave a complete conversion of starting material within 7 h (Scheme 12) (*15*). Then hydro-



Scheme 11.



Scheme 12.

Table 4. Comparison of old and new routes.

	Old route	New route	Environmental consideration
E-factor	135 kg/kg	74 kg/kg	45% less wastes
Number of synthetic steps	4	2	Less energy and wastes
Cryogenic conditions	−78°C	None	Less energy
Special material handling	LAH	None	Safety
Oxidation state adjustment	2	None	Less wastes
Cycle time	Five weeks	Two weeks	Less time, manpower and energy

lysis/decarboxylation proceeded smoothly to give product **22** in 71% yield within 2 h at 45°C (vs several days at 40°C in CH_2Cl_2).

The E-factor of the new two-step process is 74 kg/kg (45% less wastes, Table 4). The cycle time is shortened from five weeks to only two weeks. We were also able to remove the cryogenic step and the LAH reduction, rendering the process safer and environmentally more friendly.

Conclusion

In summary, we have presented an in-depth analysis of three projects from our recent programs. In all three cases, dramatic reductions in E-factors were achieved (Figure 2), mainly by shortening the synthetic routes and by implementing newly developed synthetic methodologies. It is indeed our observation that new synthetic method development is still one of the most effective ways to cut cost, save time and reduce wastes during API production.

It is also our belief that greener processes should be and can be implemented early on in the API development cycle to maximize the benefits of having such processes. (i.e. starting with the first kilo campaigns instead of waiting until Phase II or later). Over the years, this strategy has helped us to cut cost and reduce wastes for our API production for numerous projects, thereby minimizing the environmental footprint of our activities while developing innovative life-saving medicines.

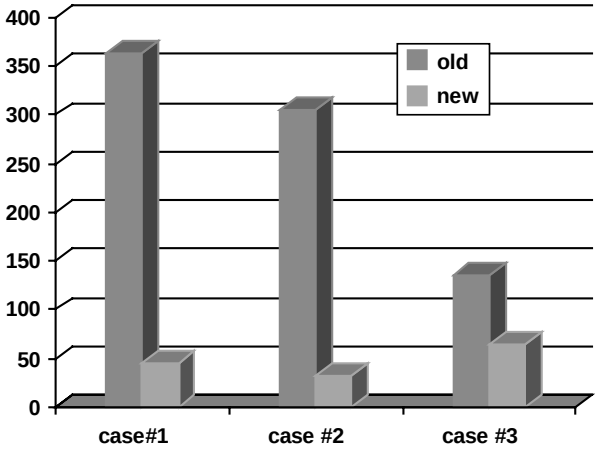


Figure 2. E-Factor reduction.

Note

1. 5-Bromo-2-iodopyridine has become commercially available in recent years from multiple vendors for only $385/kg or $110/mol. For a practical synthesis, see (*10*).

References

(1) Anantas, P.T.; Warner, J.C., Eds.; *Green Chemistry Thoery and Practice*; Oxford University Press: Oxford, 1998.
(2) (a) Sheldon, R.A. *Green Chem.*, **2007,** *9,* 1273–1283; (b) Sheldon, R.A. *Chem. and Ind.* **1992,** 903–906.
(3) Zeni, G.; Larock, R.C. *Chem. Rev.* **2006,** *106,* 4644–4680.
(4) Harcken, C.; Ward, Y.; Thomson, D.; Riether, D. *Synlett* **2005,** *20,* 3121–3125.
(5) Hands, D.; Bishop, B.; Cameron, M.; Edwards, J.S.; Cottrell, I.F.; Wright, S.H.B. *Synthesis* **1996,** 877–882.

(6) Song, J.J.; Reeves, J.T.; Gallou, F.; Tan, Z.; Yee, N.K.; Senanayake, C.H. *Chem. Soc. Rev.* **2007,** *36,* 1120–1132.
(7) Kuzmich, D.; Mulrooney, C. *Synthesis* **2003,** *11,* 1671–1678.
(8) Chambers, R.J.; Marfat, A. *Syn. Commun.* **1997,** *27,* 515–520.
(9) (a) Parham, W.E.; Piccirlli, R.M. *J. Org. Chem.* **1977,** *42,* 257–260; (b) Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. *Tetrahedron Lett.* **1999,** *40,* 4339–4342; (c) Mase, T.; Houpis, I.N.; Akao, A.; Dorziotis, I.K.; Hoang, T.; Iida, T.; Itoh, T.; Kamei, K.; Kato, S.; Kato, Y.; Kawasaki, M.; Lang, F.; Lee, J.; Lynch, J.; Maligres, P.; Monila, A.; Nemoto, T.; Okada, S.; Reamer, R.; Song, J.Z.; Tschaen, D.; Wada, T.; Zewge, D.; Volante, R.P.; Reider, P.J.; Tomimoto, K. *J. Org. Chem.* **2001,** *66,* 6775–6786.
(10) Song, J.J.; Yee, N.K. *J. Org. Chem.* **2001,** *66,* 605–608.
(11) Song, J.J.; Yee, N.K.; Tan, Z.; Xu, J.; Kapadia, S.R.; Senanayake, C.H. *Org. Lett.* **2004,** *6,* 4905–4907.
(12) (a) Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Lett.* **2000,** *41,* 4335–4338; (b) Doudouh, A.; Woltermann, C.; Gros, P.C. *J. Org. Chem.* **2007,** *72,* 4978–4980.
(13) Kuzmich, D.; Kirrane, T.; Proudfoot, J.; Bekkali, Y.; Zindell, R.; Beck, L.; Nelson, R.; Shih, C.-K.; Kukulka, A.J.; Paw, Z.; Reilly, P.; Deleon, R.; Cardozo, M.; Nabozny, G.; Thomson, D. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 5025–5031.
(14) (a) Boivin, J.; El Kaim, L.; Zard, S.Z. *Tetrahedron Lett.* **1992,** *33,* 1285–1288; (b) Boivin, J.; El Kaim, L.; Zard, S.Z. *Tetrahedron* **1995,** *51,* 2573–2584; (c) Boivin, J.; El Kaim, L.; Zard, S.Z. *Tetrahedron* **1995,** *51,* 2585–2592.
(15) (a) Reeves, J.T.; Gallou, F.; Song, J.J.; Tan, Z.; Lee, H.; Yee, N.K.; Senanayake, C.H. *Tetrahedron Lett.* **2007,** *48,* 189–192; (b) Song, J.J.; Reeves, J.T.; Roschangar, F.; Tan, Z.; Yee, N.K. Patent number WO 2007040959 A1.