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A Pd-Catalyzed Heteroannulation Approach to 2,3-Disubstituted Furo[3,2-*c*]coumarins

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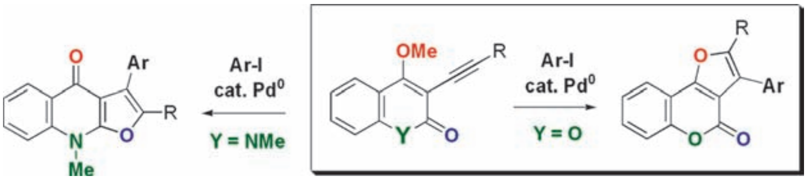
ABSTRACT



The Pd-catalyzed cyclofunctionalization of 3-alkynyl-4-methoxycoumarins with aryl halides resulted in the selective formation of 3-arylfuro[3,2-*c*]coumarins in lieu of the expected regioisomeric 3-arylfuro[2,3-*b*]chromones. A mechanism involving the linear to angular rearrangement of a Pd-containing furan intermediate was proposed.

The furan structure is a ubiquitous subunit in a variety of bioactive natural products and synthetic materials, including agrochemicals and pharmaceuticals.[1] Thus, the development of efficient and concise synthetic methods that allow access to functionalized furan derivatives, and particularly furan-fused heterocyclic compounds, remains an important task in modern organic chemistry. Significant advances in this area have resulted from the design and discovery of flexible electrophilic heteroannulations of α-alkynyl carbonyl compounds that allow the single-step construction and functionalization of the furan ring.[2] Our recent contributions to this field have targeted the synthesis of furo[2,3-*b*]pyridin-4(1*H*)-ones and related furoquinolinones (**II**) through Pd-catalyzed or iodonium-promoted cyclofunctionalization of 3-alkynyl-4-alkoxy(benzo)pyridin-2-ones (**I**) followed by in situ dealkylation of the resulting, and otherwise stable, (benzo)pyridinium salts (Scheme 1, eq 1).[3] In an effort to broaden the scope of this class of annulations, we envisioned that similar chemistry would also apply to the heteroannulation of alkynyl coumarins (**III**) and would thereby enable access to the so far poorly documented[4] furo[2,3-*b*]chromones (**IV**) (Scheme 1, eq 2). In this paper, we report our preliminary results toward this goal.

The participation of alkynylcoumarins in our Pd-catalyzed cyclofunctionalization process[3a] was first investigated. To this end, a range of starting 3-alkynyl-4-methoxycoumarins **2a−d** were readily prepared by Pd-catalyzed cross-coupling

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[1] (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (c) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.

[2] For leading references, see: (a) Rao, M. S.; Esho, N.; Sergeant, C.; Dembinski, R. *J. Org. Chem.* **2003**, *68*, 6788. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679. (c) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609. (d) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (e) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (f) Zhao, L.; Cheng, G.; Hu, Y. *Tetrahedron Lett.* **2008**, *49*, 7364.

[3] (a) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441. (b) Aillaud, I.; Bossharth, E.; Conreaux, D.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2006**, *8*, 1113.

[4] A limited number of 3-unsubstituted furo[3,2-*b*]chromones have been recently reported; see, for instance: (a) Lee, Y. R.; Suk, J. Y. *Tetrahedron* **2002**, *58*, 2359. (b) Tollari, S.; Palmisano, G.; Cenini, S.; Cravotto, G.; Giovenzana, G. B.; Penoni, A. *Synthesis* **2001**, 735. (c) Kobayashi, K.; Sakashita, K.; Akamatsu, H.; Tanaka, K.; Uchida, M.; Uneda, T.; Kitamura, T.; Morikawa, O.; Konishi, H. *Heterocycles* **1999**, *51*, 2881. (d) Lee, Y. R.; Kim, B. S.; Wang, H. C. *Tetrahedron* **1998**, *54*, 12215. (e) Lee, Y. R.; Byun, M. W.; Kim, B. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 1080.

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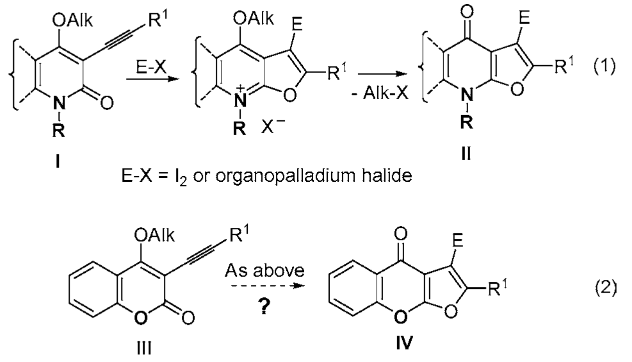
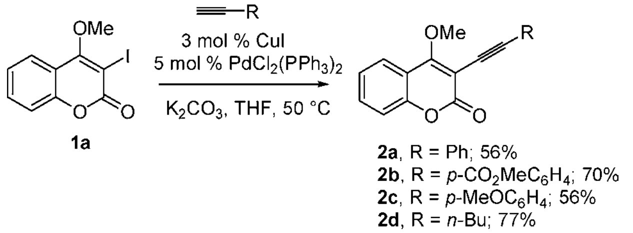
Scheme 1. Heteroannulative Strategies toward Fused Furans



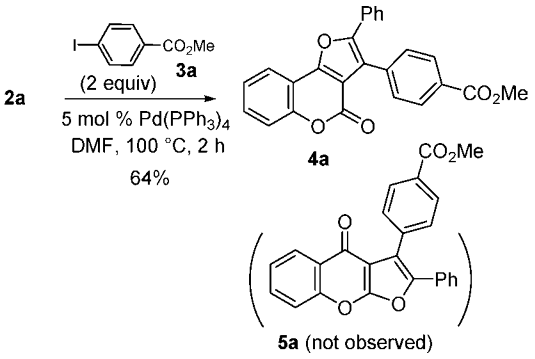
reactions of 3-iodo-4-methoxycoumarins with terminal acetylenes under amine-free conditions (Scheme 2).[5]

Scheme 2. Synthesis of 3-Alkynyl-4-methoxycoumarins



Preliminary studies were conducted using 4-methoxycoumarin **2a** and (p-MeO$_2$C)-phenyl iodide **3a** as model substrates. Initially, the cyclization reaction was probed using our previous conditions, that is to say cat. PdCl$_2$(PPh$_3$)$_2$ reduced by n-BuLi, as Pd(0) catalyst, in refluxing MeCN. However, no reaction was observed under these conditions even after prolonged reaction times (24 h). Pleasingly, a rapid screening of Pd catalysts and solvents led us to isolate a cyclization compound that had incorporated the aryl fragment. Surprisingly, however, IR and NMR experiments suggested that we had in fact isolated the angularly fused furo[3,2-*c*]coumarin **4a** (Scheme 3), the structure of which was confirmed by X-ray analysis (Figure 1). Pd(PPh$_3$)$_4$ was found to be a particularly effective catalyst for this transformation when used in DMF at 100 °C. Under these conditions, **4a** was obtained in a satisfactory 64% yield within 2 h reaction time. Furo[3,2-*c*]coumarins as well as the structurally related dihydrofurocoumarins and coumestans are valuable compounds endowed with many interesting biologically properties.[6,7] We therefore sought to investigate the unexpected behavior of alkynyl coumarins in this cyclization process more deeply.

Scheme 3. Coupling−Heteroannulation of **2a** with **3a**



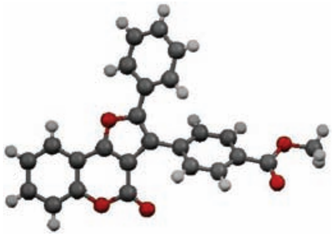


Figure 1. X-ray analysis of **4a**.

The generality of the process was first explored with various organic halides (Table 1). Moderate to good yields were generally obtained with aryl halides bearing electron-withdrawing groups. Conversely, as illustrated with the reaction of p-methoxyphenyl iodide, the presence of an electron-donating group on the aryl coupling partner resulted in poor yields of the desired furocoumarins, probably reflecting a decreased electrophilicity of the organoPd(II) complex (Table 1, entry 5). A range of substituted aryl as well as alkyl groups on the alkyne were also successfully employed in the cyclization−coupling reaction (Table 1, entries 7−10 and 11, respectively).

Interestingly, 3-methylfurocoumarin **6** was often isolated as a side product (<30% isolated yield). It is likely that

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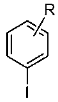
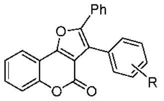
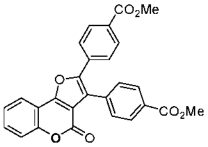
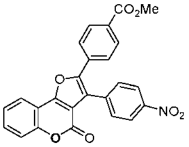
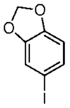
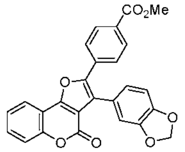
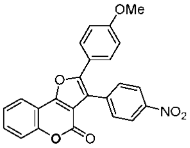
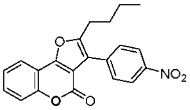
(5) This avoids undesired amine-induced demethylation of the resulting acetylenic coumarins; see: (a) Conreaux, D.; Belot, S.; Desbordes, P.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2008**, *73*, 8619. (b) Le Bras, G.; Radanyi, C.; Peyrat, J.-F.; Brion, J.-D.; Alami, M.; Marsaud, V.; Stella, B.; Renoir, J.-M. *J. Med. Chem.* **2007**, *50*, 6189.

(6) (a) Wang, X.; Nakagawa-Goto, K.; Kozuka, M.; Tokuda, H.; Nishino, H.; Lee, K.-H. *Pharm. Biol.* **2006**, *44*, 116. (b) Mulholland, D. A.; Iourine, S. E.; Taylor, D. A. H.; Dean, F. M. *Phytochemistry* **1998**, *47*, 1641. (c) Motai, T.; Kitanaka, S. *Chem. Pharm. Bull.* **2004**, *52*, 1215. (d) Lee, Y. R.; Kim, B. S.; Wang, H. C. *Tetrahedron* **1998**, *54*, 12215. (e) Pôças, E. S. C.; Lopes, D. V. S.; da Silva, A. J. M.; Pimenta, P. H. C.; Leitão, F. B.; Netto, C. D.; Buarque, C. D.; Brito, F. V.; Costa, P. R. R.; Noël, F. *Bioorg. Med. Chem.* **2006**, *14*, 7962.

(7) From a synthetic point of view, 2,3-disubstituted furocoumarins have been the focus of recent attention. For leading references, see: (a) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285. (b) Cadierno, V.; Diez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852. (c) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732. (d) Huang, W.; Wang, J.; Shen, Q.; Zhou, X. *Tetrahedron* **2007**, *63*, 11636. (e) Nair, V.; Menon, R. S.; Vinod, A. U.; Viji, S. *Tetrahedron Lett.* **2002**, *43*, 2293. (f) Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Tetrahedron Lett.* **2001**, *42*, 3503. (g) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Org. Lett.* **2000**, *2*, 1387. (h) Ahluwalia, V. K.; Adhikari, R.; Singh, R. P. *Synth. Commun.* **1985**, *15*, 1191. In many cases, mixtures of isomeric furo[3,2-*c*]coumarins and furo[3,2-*b*]chromones have been previously obtained: see ref 4.

Table 1. Synthesis of 3-Arylfuro[3,2-*c*]coumarins[a]

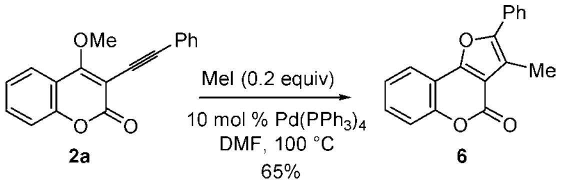
entry	alkynyl coumarin	organic halide	furocoumarin (yield %)[b]
			
1	**2a**	**3a**; R = *p*-CO$_2$Me	**4a**; 64
2	**2a**	**3b**; R = *p*-NO$_2$	**4b**; 82
3	**2a**	**3c**; R = *p*-F	**4c**; 52
4	**2a**	**3d**; R = H	**4d**; 49
5	**2a**	**3e**; R = *p*-OMe	**4e**; 6
6	**2a**	**3f**; R = *m*-CF$_3$	**4f**; 82
7	**2b**	**3a**	 **4g**; 92
8	**2b**	**3b**	 **4h**; 87
9	**2b**	 **3g**	 **4i**; 35
10	**2c**	**3b**	 **4j**; 65
11	**2d**	**3b**	 **4k**; 64[c]

[a] All reactions were run on a 0.2 mmol scale using 2 equiv of aryl iodide in 2 mL of DMF. [b] Isolated yields. [c] Not isolated as a pure compound. Contains small amounts of inseparable 4,4′-dinitro-1,1′-biphenyl.

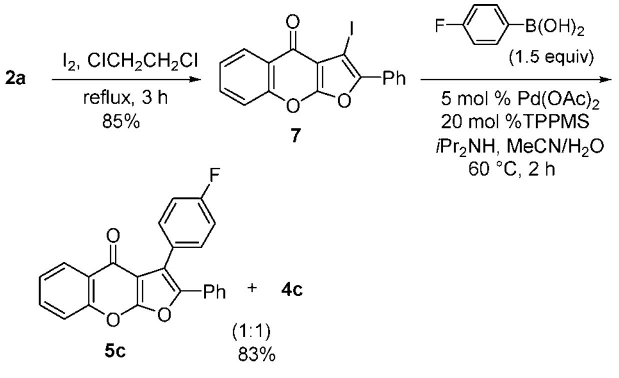
cycloisomerization of **2a** occurred via competitive activation of the triple bond by a methylpalladium(II) iodide complex, resulting in methylation of the furan ring following cyclization. This complex would be generated by oxidative addition of methyl iodide, produced in the demethylation step (vide infra), to Pd(0). Remarkably, reaction of **2a** under the previous conditions in the presence of only 0.2 equiv of MeI as an initiator of the cyclization process led to the production of **6** in 65% isolated yield (Scheme 4).

From a mechanistic point of view, we believed that the alkynyl coumarins behave similarly to alkynyl pyridones[3a] in the first steps of the cyclization process, undergoing intramolecular attack by the carbonyl oxygen of the ester group to give a linearly fused furan intermediate which, at some point, would rearrange to its angularly fused isomeric form.[8] To investigate this hypothesis, we first needed to seek a method for preparing furochromones of type **5** so as to probe their stability under the cyclization reaction conditions. We thus turned our attention to the alternative iodocyclization approach to 3-substituted furan derivatives.[3b] Pleasingly, it was found that 3-alkynylcoumarin **2a** reacted with 2 equiv of I$_2$ in refluxing 1,2-dichloroethane to directly afford[9] the expected 3-iodofurochromone **7** in 85% isolated yield as the sole reaction product.[10] Interestingly, Suzuki−Miyaura cross-coupling of **7** with *p*-fluorophenyl boronic acid using the system Pd(OAc)$_2$/TPPMS/*i*-Pr$_2$NH in aqueous MeCN produced a 1:1 mixture of regioisomeric furan derivatives **4c** and **5c** isolated in 42% and 41% yield, respectively. Importantly, this isomeric ratio did not evolve with time. Besides, **5c** proved stable when subjected to reaction conditions similar to those previously used for the synthesis of **4c** from **2a** (2 equiv of *p*-FPhI, 10 mol % of Pd(PPh$_3$)$_4$, DMF, 100 °C), which indicated that **5c** is probably not an intermediate in the synthesis of **4c** (Scheme 5).

Scheme 4. MeI-Initiated Cycloisomerization of **2a**



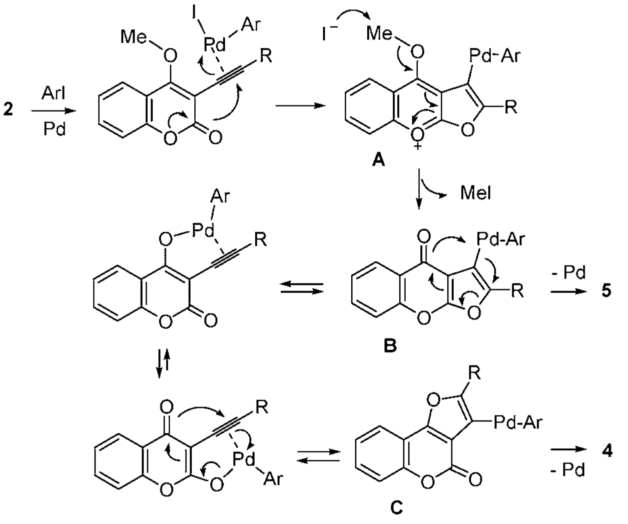
Scheme 5. Access to Furochromone **5c** via Iodocyclization



TPPMS: Triphenylphosphine monosulfonate

In light of the previous observations, we may propose the mechanistic pathway described in Scheme 6 to explain the formation of angularly fused furan derivatives either via Pd-catalyzed cyclization or Suzuki−Miyaura cross-coupling. In the cyclization process, the σ-arylPd(II) iodide complex generated in situ by oxidative addition of the organic iodide to the Pd(0) catalyst would activate the alkyne triple bond of **2a** toward nucleophilic attack of the ester carbonyl oxygen

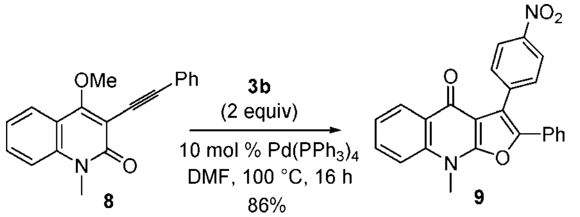
Scheme 6. Mechanistic Proposal



to give the intermediate furochromenylium salt **A**. Demethylation of the latter would proceed rapidly through attack of the methoxy group by the halide counterion before reductive elimination takes place to give the corresponding Pd-containing furochromone **B** as a key intermediate along with iodomethane as side product.[11] Intermediate **B** is also expected to be produced in the Suzuki−Miyaura cross-coupling reaction. It may evolve through reductive elimination to furnish the linearly fused furan derivatives **5** or possibly rearrange to the isomeric Pd-containing furocoumarin **C** via a furan ring-opening[12]−furan ring-closure pathway involving palladium enolate intermediates. Reductice elimination would then afford the angularly fused furan derivatives **4**.[13]

It is worth noting that, under identical cyclization reaction conditions, alkynyl quinolinone **8** reacted uneventfully with aryl iodide **3b** to furnish the linearly fused furoquinolinone **9** as the sole cyclization−coupling product in 86% isolated yield (Scheme 7), the structure of which was secured by X-ray analysis. It is likely that in this case reductive elimination would be faster than demethylation possibly due to a better stability of the putative linearly fused furoquinolinium salt intermediate (not shown).

Scheme 7. Heteroannulation of Alkynyl Quinolinone **8**



In summary, we have unraveled the flexibility provided by electrophilic heteroannulation reactions of 3-alkynyl-4-alkoxycoumarins, which hold the synthetic potential to access either furo[3,2-*c*]coumarins or the regioisomeric furo[2,3-*b*]chromones. Further studies into the scope and limitations as well as the mechanistic understanding of this chemistry are currently underway in our laboratories and will be reported as events merit.

Acknowledgment. This research was assisted financially by a grant to G.R. from the French Ministry of Higher Education and Research (MESR). We thank Dr. E. Jeanneau (Centre de Diffractométrie Henri Longchambon, Université Lyon 1) for the X-ray crystallographic analyses. S. Belot (Université Lyon 1) is acknowledged for preliminary experiments.

Supporting Information Available: Experimental procedures, characterization for all compounds, and X-ray data for compounds **4a** and **9** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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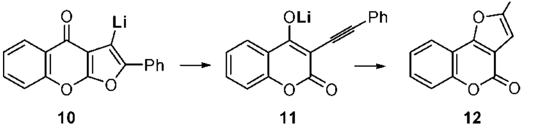
(8) Linear to angular rearrangements have been previously reported, especially in the case of dihydrofuroquinolinones: (a) James, K. J.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1467. (b) Butenschön, I.; Möller, K.; Hänsel, W. *J. Med. Chem.* **2001**, *44*, 1249. (c) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719. (d) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642. The rearrangement of dihydrofurochromones to thermodynamically more stable dihydrofurocoumarins has also been documented. (e) Majumdar, K. C.; Choudhury, P. K.; Nethaji, M. *Tetrahedron Lett.* **1994**, *35*, 5927.

(9) The formation of the putative furochromenylium salt intermediate could not be observed under these conditions probably due to low stability.

(10) Interestingly, **2a** was shown to undergo simple *trans*-addition of I$_2$ to the triple bond at room temperature. However, formation of the desired iodofuran was found to occur at higher temperatures, suggesting that this addition reaction may then become reversible: Miller, S. I.; Noyes, R. M. *J. Am. Chem. Soc.* **1952**, *74*, 3403. This process is currently under investigation and details will be reported in a forthcoming paper.

(11) At the present time, we cannot unequivocally rule out the possibility that demethylation may occur prior to cyclization. However, the starting coumarin **2a** proved stable when heated in DMF at 100 °C for several hours, even in the presence of Pd(PPh$_3$)$_4$ or Pd^{II} salts.

(12) Ring-opening processes have already been observed in the case of 3-lithiobenzofurans and 3-lithiofuropyridines; see, respectively: (a) Barton, T. J.; Groh, B.; L, *J. Org. Chem.* **1985**, *50*, 158, and references therein. (b) Shiotani, S.; Morita, H. *J. Heterocycl. Chem.* **1992**, *29*, 413. See also: (c) Gribble, G. W.; Saulnier, M. G. *J. Org. Chem.* **1983**, *48*, 607. (d) Frejd, T.; Karlsson, J. O.; Gronowitz, S. *J. Org. Chem.* **1981**, *46*, 3132. Interestingly, treatment of iodofurochromone **7** with 1.1 equiv of *n*-BuLi (THF at −78 °C, 3 h) followed by quenching with saturated aq NH$_4$Cl at rt led to the formation of furocoumarin **12** (20% conversion as determined by ^{1}H NMR). It is likely that **12** resulted from ring-opening of 3-lithiofurochromone **10** leading to enolate intermediate **11** which then underwent anionic cyclization as previously observed (see ref 5a).



(13) Further work will be undertaken to investigate factors that may influence the product distribution in the Suzuki reaction so as to possibly drive this reaction toward the selective formation of the desired linearly fused products. This would also provide additional information concerning the isomerization process.