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Carboxylation reaction of a highly functionalized vinylic anion: a case of unexpected stability and reactivity

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ABSTRACT

Attempts to prepare JNJ 26273364, a highly functionalized pyrazole-based CCK_1 receptor antagonist, using a carboxylation reaction led to a series of unexpected results. This work demonstrated the unique reactivity and stability of the highly functionalized *Z*-alkene functionality present around the pyrazole.

1. Introduction

In previous publications from our laboratories, structure–activity relationships (SAR) of a novel series of pyrazole-based CCK_1[1–4] receptor antagonists were described.[5] This work led to the discovery of JNJ 26273364 (Fig. 1) as a potent, safe and selective antagonist. As part of our continuing chemistry efforts, an alternative synthetic route to this analog was required in order to optimize the overall chemical yield. Our initial goal was to develop a synthetic route that would require the use of a versatile intermediate which could be used for additional applications. Indeed, accessing such an intermediate would allow the medicinal chemists to apply divergent syntheses in order to obtain various analogs with distinct structural modifications. In addition, the route should enable a facile preparation of ^{14}C radiolabeled material required to profile and measure the absorption, distribution, metabolism, and elimination of the compound in animals (rats and dogs).

The highly functionalized pyrazole possesses a unique trisubstituted *Z*-alkene functionality. Two of the major challenges associated with the synthesis of this functional group are (1) to utilize a synthetic route which will afford the product with high stereoselectivity and (2) to identify reaction conditions that are sufficiently mild to avoid any isomerization. Three major synthetic routes have been developed to access such α,β-unsaturated carboxylic acid moieties in the scientific literature. The most common strategies involve the use of aromatic aldehydes in the Perkin reaction,[6] or substituted malonic acids through the (Doebner) Knoevenagel reaction.[7] Although these methods have been widely used, they primarily suffer from a poor selectivity generally favoring the *E*-isomer. Alternatively, α,β-unsaturated carboxylic acids can be accessed from the Horner–Wadsworth–Emmons phosphonoacetate reagents after hydrolysis of the esters.[8] However, this approach necessitates the preparation of the individual reagents, and the ester products can isomerize under the reaction conditions. To overcome these liabilities, we thought that a sequential functionalization of a geminal dibromo-vinyl group could be a valuable synthetic approach. We wish to discuss herein the results of our various investigations toward the development of a carboxylation reaction of a highly functionalized alkene.

2. Results and discussion

Originally, JNJ 26273364 was synthesized in six steps as shown in Scheme 1.[5c,9] The major drawback from the original medicinal chemistry route was that the light-promoted isomerization of the *E*-alkene.

Indeed, this transformation provided the desired *Z*-alkene **1** in low conversion (15% isolated yield) along with the *E*-alkene **7** as the major isomer (20% isolated yield) (Scheme 1). In order to address this problem, a new approach to the synthesis of this material was explored.

We envisioned that JNJ 26273364 (**1**) could be prepared from the key intermediate vinyl bromide **9** in a single step using a lithium–halogen exchange reaction followed by carboxylation of the corresponding vinylic anion (Fig. 2).

To first evaluate the validity of our initial strategy we decided to access the precursor **9** from JNJ 26273364 itself (**1**), available in-house in large quantities using a halodecarboxylation reaction of

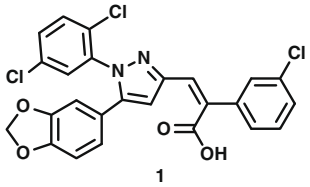

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Figure 1. JNJ 26273364.

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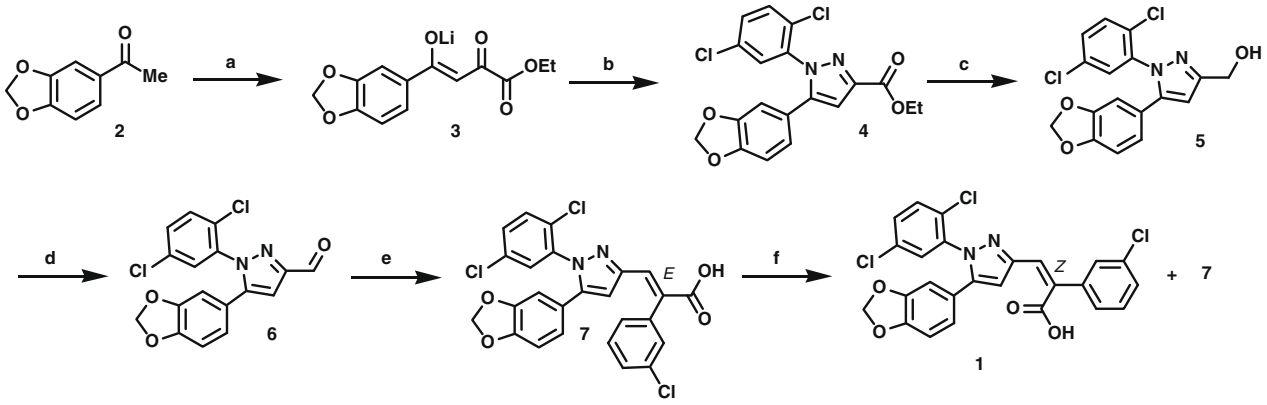


Scheme 1. Original medicinal chemistry synthesis. Reagents and conditions: (a) diethyl oxalate, LiHMDS, Et_2O, −78 °C to rt; (b) 2,5-dichlorophenylhydrazine, THF, TsOH, 40 °C, 74% over 2 steps; (c) DIBAL, THF, −78 °C to rt, 96%; (d) Dess–Martin periodinane, DCM, rt, 99%; (e) 3-chlorophenylacetic acid, NEt_3, Ac_2O, rt, 49%; (f) UV light, $CHCl_3$, yields: **1** (15%) and **7** (20%).

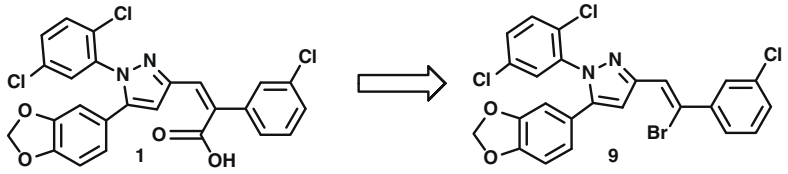
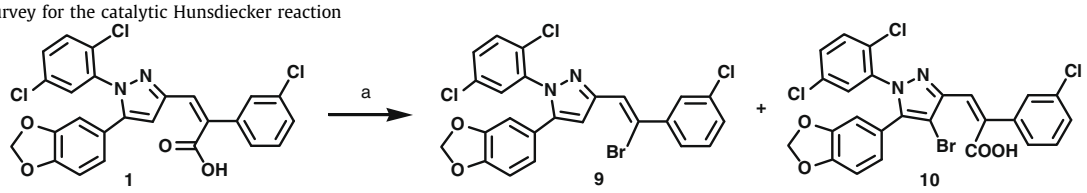


Figure 2. Proposed key transformation.

Table 1
Catalyst/solvent survey for the catalytic Hunsdiecker reaction



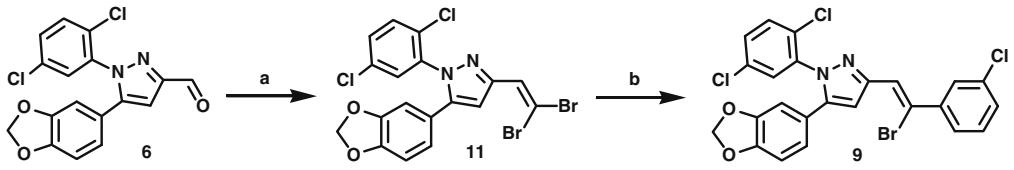
Entry	Catalyst	Solvent	Products	Yields
1	NEt_3	DCM	**10**	92[a]
2	$Bu_4N^+OAc^-$	DCE	**10**	100[b]
3	$Bu_4N^+OAc^-$	MeCN/H_2O (97:3)	**10**	100[b]
4	$Bu_4N^+OC(O)CF_3^-$	DCE	**10**	100[b]
5	LiOAc	MeCN/H_2O (97:3)	**10**	100[b]

Reagents and conditions: (a) NBS, rt, 5 min.
[a] Isolated yield.
[b] Determined by HPLC.

α,β-unsaturated carboxylic acids (catalytic Hunsdiecker reaction) (Table 1).

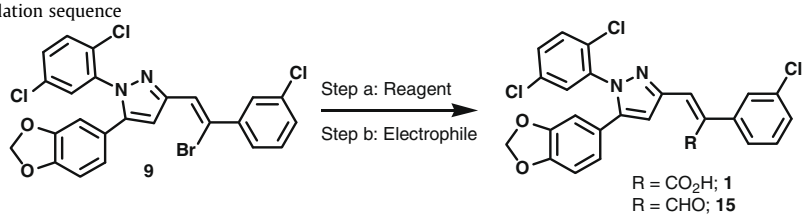
Treatment of compound **1** with a catalytic amount of triethylamine in dichloromethane followed by addition of *N*-bromosuccinimide rapidly afforded the corresponding brominated pyrazole **10** in 92% yield with no trace of desired product **9** (Table 1, entry 1). Attempts to favor the desired halodecarboxylation event by increasing the rate of the reaction using alternative catalysts and/or solvents (including LiOAc and MeCN/H_2O as suggested from the literature[10]) did not lead to detectable amounts of desired product (Table 1).

An alternative synthesis of the key intermediate **9** was devised which involved the use of pyrazole-3-carbaldehyde **6** as the starting material (Scheme 2). This compound was also readily available



Scheme 2. Corey-Fuchs/Suzuki strategy for the synthesis of intermediate **9**. Reagents and conditions: (a) PPh_3/CBr_4, DCM, 0 °C, 20 min; (b) 3-chlorophenyl boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O (4:1), 70 °C, 12 h, 78%.

Table 2
Lithium–bromide exchange/carboxylation sequence



Entry	Reagents	Electrophile	*T* (°C)	Time (min)		Results
				a[a]	b[b]	
1	*tert*-BuLi	CO_2 gas	−78	2	10	**9** + ND
2	*tert*-BuLi	Dry ice	−78	2	10	**9** + ND
3	*tert*-BuLi	CO_2 gas	−78	5	10	ND
4	*n*-BuLi/TMEDA	CO_2 gas	−78	10	10	**9** + ND
5	*i*-PrMgCl	CO_2 gas	25	120	120	**9**
6	$Pd(OAc)_2$/dppf/MeOH/DMF	CO gas	50	24 h	120	**9**
7	$PdCl_2/PPh_3$ NBu_3/H_2O	CO gas	70			ND

[a] Reaction time for step a.
[b] Reaction time for step a; ND: presence of unknown byproducts.

in-house as a precursor to JNJ 26273364. Treatment of **6** with triphenylphosphine and carbon tetrabromide in dichloromethane at 0 °C for 20 min afforded after flash column chromatography the desired product **11** in 99% yield. A subsequent Suzuki cross-coupling reaction in the presence of tetrakis(triphenylphosphine)palladium and 3-chloro-phenylboronic acid provided the *Z*-alkene product **9** as a single stereoisomer in 78% isolated yield. The stereochemistry of the alkene was unambiguously assigned using 2D NMR spectroscopy and NOESY studies.

Lithium–bromide exchange of the vinyl bromide **9** was the key step. This transformation was investigated using various reagents, solvents, and temperatures. The results are shown in Table 2. Our initial attempt involved the use of *tert*-butyl lithium for 2 min at −78 °C followed by addition of CO_2 gas. Under these reaction conditions, recovered starting material along with uncharacterized byproducts was detected (entry 1). Similar results were obtained when CO_2 gas was replaced with dry ice (entry 2). Increasing the lithium–bromide exchange reaction time (step a) from 2 to 5 min led to complete consumption of the starting material but no trace of product (entry 3). Using alternative bases, such as *n*-butyl lithium with TMEDA (entry 4) or *i*-PrMgCl (entry 5) were also unsuccessful as the desired product was not detected. To probe the reactivity of the precursor **9** to undergo carbonylation reaction, two sets of conditions were investigated using different palladium catalysts in the presence of CO gas (entries 6 and 7). Unfortunately, none of these reactions afforded the desired aldehyde product **15**.

Isolation and 2D NMR structural determination of the common major byproduct from the reactions revealed compound **12** (Fig. 3) which is a constitutional isomer of the targeted compound **1**. With the assumption that the formation of compound **12** follows the proposed mechanism (Fig. 3), a few observations can be made: (1) the lithium–bromide exchange was indeed occurring, (2) the vinylic anion was unstable under the reaction conditions and (3) deprotonation of the aryl ring (inter- or intramolecular) appeared to be favored, leading to CO_2 incorporation at the aromatic ring instead of at the vinylic group (Fig. 3).

It was hypothesized that reaction conditions that would allow for a greater stability of the vinylic anion (intermediate **i**) should provide, after quenching with CO_2, good conversion to the desired product. Two variables (i.e., temperature and reaction time) were examined and the results are summarized in Table 3. Using a mixture of THF/Et_2O/pentane (4:1:1; so-called Trapp mixture) and Et_2O/liquid nitrogen, intermediate **9** was treated with *tert*-butyl lithium at −116 °C for 1 min followed by addition of CO_2 gas or dry ice. Under these conditions, none of the rearranged product **12** was isolated and 15% of the desired product was isolated along with recovered starting material and unsubstituted alkene **13** (Table 3, entry 1). It should be noted that no isomerization to the *E*-alkene was observed under these reaction conditions. This result

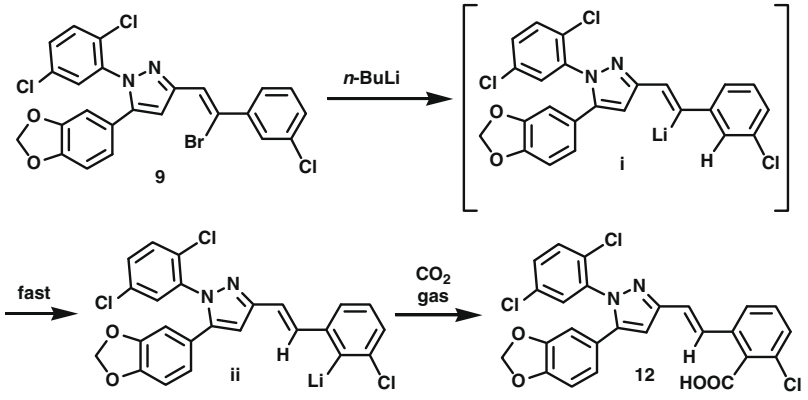
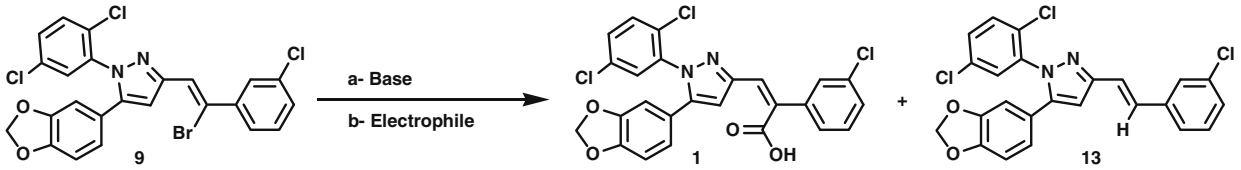


Figure 3. Proposed mechanism for the formation of **12**.

Table 3
Optimization of the lithium–bromide/carboxylation reaction[a]



Entry	Base	Reaction time (min) Step a/step b	*T* (°C)	Electrophile	% Conversion		
					1	**9**	**13**
1	*tert*-BuLi	1/20	−116	CO_2 gas or dry ice	15	8	77
2	*tert*-BuLi	5/20	−116	CO_2 gas	71 (48[b])	0	0

[a] All reactions were carried out under the following reaction conditions: 1.2 equiv of base in a THF/Et_2O/pentane mixture (4:1:1) at the indicated temperature under N_2 atmosphere.
[b] Isolated yield.

suggested that at very low temperature (−116 °C), the stability of the vinyl anion had been improved but that the lithium–bromide exchange reaction had become slower. The reaction time was extended to 5 min and under these conditions the desired JNJ 26273364 was isolated in 48% yield after flash column chromatography (Table 3, entry 2).

In summary, a stereoselective synthesis of JNJ 26273364 was developed which involved a carboxylation reaction of intermediate **9**. The study conducted for the synthesis of this key starting material **9** led to the design of a tandem Corey-Fuchs/Suzuki sequence to afford the desired *Z*-alkene as a single stereoisomer. Optimization of the lithium–bromide exchange reaction required very low temperature (−116 °C) in order to stabilize the vinyl anion. Upon quenching the reaction mixture with CO_2 gas, the *Z*-alkene isomer was isolated in 48% isolated yield without any trace of isomerization product. This protocol was also successfully applied to the synthesis of [^{14}C]-labeled JNJ 26273364 from $^{14}CO_2$ in a single step.[11] This method highlights the fact that despite the high degree of functionalization of the triarylpyrazole precursor **9**, carefully chosen reaction conditions were identified that allowed for the regiospecific carboxylation reaction. This temperature controlled transformation could also be expanded to other types of electrophiles which could in turn facilitate our medicinal chemistry efforts.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures and characterization data for all unknown compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.112.

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11. Experimental details for the preparation of [^{14}C]-labeled JNJ 26273364 can be found in the Supplementary data.