Tetrahedron Letters 50 (2009) 2119–2120

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Radical additions to allyl bromides. A synthetically useful, 'Tin-Free' method for carbon–carbon bond formation

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ARTICLE INFO

Article history:
Received 10 December 2008
Revised 11 February 2009
Accepted 19 February 2009
Available online 25 February 2009

ABSTRACT

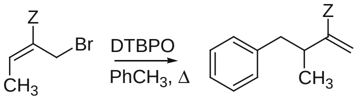
The scope and limitations of a novel free radical chain process involving the addition of benzyl radicals to substituted allyl bromides were examined and extended to explore the effect of α-substitution on the allyl bromide (R′), and the use of pyrrolidine amides and oxazolidinone as activating substituents (Z) as the first steps toward the development of a stereoselective, radical-based C–C bond-forming reaction which is environmentally benign.

Benzyl and cumyl radicals readily add to various β-substituted allyl bromides **1** using peroxide initiators at elevated temperatures.[1] This reaction is unique because it does not rely on the use of toxic metals for free radical generation.[2] The reaction mechanism involves hydrogen abstraction by $Br^{\cdot}$ producing a benzylic radical ($R^{\cdot}$), which subsequently adds to the allyl bromide. β-Elimination of $Br^{\cdot}$ completes the chain radical (Scheme 1). Earlier work focused on additions to relatively simple allyl bromides, Z = H, Ph, CO_2Et, and CN. We now expand on this theme to include methyl ester, pyrrolidine amide, and oxazolidine functional groups. Also, to explore the viability of developing this reaction into a stereoselective process, we studied additions of prochiral radicals (using ethyl benzene as our radical precursor) and α-methyl-substituted allyl bromides.

The mode of initiation of these reactions involves H-abstraction by the initiating radical ($In^{\cdot}$) from the starting alkylaromatic. Di-*t*-butylperoxide (DTBPO) has proven to be an especially effective initiator because $^{t}BuO^{\cdot}$ does not add readily to double bonds.

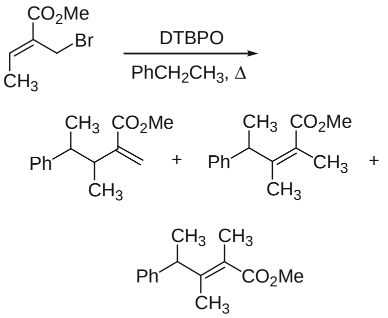
The results of this study are summarized in Table 1. Overall, yields were typically 50% or greater lending credence to the synthetic usefulness of this reaction. With allyl bromide (Z = H, entry a), the absence of an activating substituent leads to low yields and low reaction rates (only 33% yield after 94 h). However, when Z is a strong electron-withdrawing group (e.g., Z = CN, CO_2R), the reaction gave good yields over a short reaction time with both cumyl and benzyl radicals (entries j and k). Because of their affinity toward electrophilic substrates, alkyl radicals have been described as being nucleophilic.[3]

This reaction was expanded to include α-methyl-substituted allyl bromides where Z was either a methyl ester or a pyrrolidine amide (Eq. 1). The yields for these reactions using toluene were 57% for the methyl ester (13 h) and 69% for the pyrrolidine amide (12 h). The use of ethyl benzene in an analogous reaction resulted in a complex mixture of products including some with rearranged carbon-carbon double bonds (Eq. 2).



(1)

Kinetic chain lengths were determined by comparing the rate of product formation with respect to the rate of initiator disappearance.[4] These experiments were carried out in the presence of 1,2-epoxybutane as an HBr scavenger. The chain length data are summarized in Table 2.



(2)

Relative rates of addition of $PhCH_2^{\cdot}$ to the various allyl bromides were determined by competition experiments. The results of these studies are summarized in Table 3. These data are similar to those described by Giese, attributable to a β-effect, and demonstrate that the overall rate increases with the electron-withdrawing ability of

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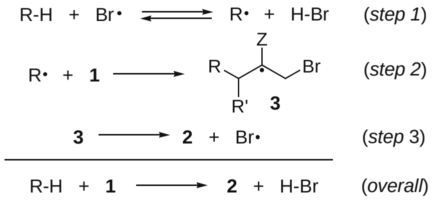
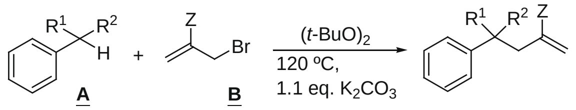
doi:10.1016/j.tetlet.2009.02.154



Scheme 1. Mechanism of radical-based allyl transfer reaction.

Table 1
Additions of benzyl radicals to substituted allyl bromides



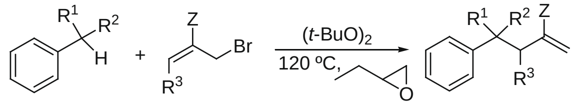
Entry	R^1	R^2	Z	A (mmol)[a]	B (mmol)	Time (h)	Yield (%)
a[b]	H	H	H	47	0.69	94	33
b	H	H	Ph	47	0.72	93	82
c	H	H	Ph	2.8[d]	0.72	93	24
d	CH_3	CH_3	Ph	36	0.72	93	100
e[c]	CH_3	CH_3	Ph	1.4[d]	0.72	93	66
f	H	H	CO_2Et	47	0.77	40	47
g	CH_3	CH_3	CO_2Et	36	0.77	94	48
h	H	H	CO_2Me	190	3.0	3	63
i	H	CH_3	CO_2Me	160	3.0	3	57
j[b,c]	H	H	CN	38	0.77	2	66
k[b]	CH_3	CH_3	CN	29	0.77	2	80
l	H	H	COPyr	190	3.0	4	72
m	H	CH_3	COPyr	160	3.0	5	66
n	H	H	Ox	140	2.2	8	53
o	H	CH_3	Ox	120	2.2	10	59

[a] All reactions were performed in neat toluene, ethyl benzene, or cumene using 20 mol % di-*tert*-butylperoxide as the initiator unless otherwise noted.
[b] 1.1 equiv of 1,2-epoxybutane used as an HBr scavenger.
[c] 20 mol % benzoyl peroxide used as an initiator at 80 °C.
[d] In 5 mL benzene.

the Z substituent. Steric effects are evident by the diminished reactivity of α-methyl-substituted allyl bromides toward $\text{PhCH}_2^{\bullet}$, and by the lower chain lengths observed for these allyl bromides (Table 2). A similar phenomenon regarding the steric α-effect has been previously reported.[3c,5]

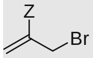
To summarize, this reaction is limited to substrates which have activating β-substituents (Z) and an unhindered α-carbon. Good yields are obtainable with α-methyl substrates at longer reaction times even though the chain-lengths for these compounds are shorter. However, only benzyl radical ($\text{PhCH}_2^{\bullet}$) adds without producing complex product mixtures, in contrast to additions of the 1-phenylethyl radical (Eq. 2). Presumably, cumyl radical would behave similarly. Pyrrolidine amides and oxazolidinone substituents are suitable activating substituents, and provide the foundation for developing new stereoselective carbon–carbon bond-forming reactions via the use of chiral Lewis acids.[6] Finally, the fact that this method does not require toxic metals such as mercury or tin for radical generation makes this reaction especially appealing from green chemistry standpoint.

Table 2
Initial chain length data for benzyl radical additions to various allyl bromides



–Z	Initial chain length (relative chain length)			
	R^1 = R^2 = H R^3 = H	R^1 = R^2 = H, R^3 = CH_3	R^1 = CH_3 R^2 = R^3 = H	R^1 = R^2 = CH_3 R^3 = H
H	10 (1)	–	–	–
Ph	400 (40)	–	–	60
CO_2Et	800 (80)	–	–	60
CO_2Me	400 (40)	50 (5)	100	–
CN	700 (70)	–	–	400
COPyr	50 (5)	3.0 (0.3)	60	–
Ox	20 (2)	–	20	–

Table 3
Relative reactivities of various allyl bromides toward $\text{PhCH}_2^{\bullet}$

 , -Z =	k_{rel} (80 °C)	k_{rel} (120 °C)
H	0.01	–
Ph	0.59	–
CO_2Me	–	0.95
CO_2Et	1	1
CN	1.6	–
COPyr	–	0.02
Ox	–	0.01

Acknowledgment

Financial support from the National Science Foundation (CHE-0548129) is acknowledged and appreciated.

Supplementary data

General and detailed experimental procedures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.154.

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4. The amount of $^t\text{BuO}^{\cdot}$ produced was calculated based on the rate constant $k = 1.72 \times 10^{-6}\ \text{s}^{-1}$ at 120 °C.
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6. For examples of chiral auxiliary controlled radical additions, see: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*, 1st ed.; VCH: New York, NY, 1996. Chapter 5, p 178.