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Lewis Acid Catalyzed Protective Opening of Epoxides with Pivaloyl Halides

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An efficient protocol of shorter reaction times for protective opening of epoxides (POE) with pivaloyl halides under solvent-free conditions in presence of Lewis acid catalysts has been developed.

Keywords: Lewis acid, Epoxides, Protective opening, Pivaloyl halides.

INTRODUCTION

Epoxides[1] are well known most versatile compounds in organic synthesis. Due to their ease of formation, wide reactivity with nucleophiles and their ability to undergo region selective ring opening[2,3] reactions contributes their synthetic value not only as final products but also as key intermediates[4,5]. Preservation and protection of the oxirane ring is one of the most important aspects during the many cases in total synthesis[6,7] of biologically active natural products[8,9]. Epoxides due to their highly strained three-membered ring and difficulties in the stability aspects they tend to react with a wide variety of reagents such as electrophiles, nucleophiles[10], acids, bases, some reducing agents and oxidizing agents[11,12]. To side step these problems, there is a substantial need for protective opening of the oxirane ring[13] into its derivatives from which it can be easily reconstructed with consistent regio-selectivity and stereo-selectivity[14,15]. Green chemical reactions have become more important in recent decades. Reactions in solvent free conditions are considerably safer, nontoxic, environmentally friendly and inexpensive. The present needs for clean, fast, efficient and selective processes have promoted the demand for metal-based reaction promoters, especially the ones that can be applied in catalytic amounts and/or that are recyclable. Shorter reaction times are of utmost importance to make the synthetic chemistry viable in many applications. Although there are many protocols for epoxide ring opening, to the best of our knowledge only one method is reported so far to prepare *vic*-halopivaloylates with pivaloyl halides[16]. Here in we are reporting the Lewis acid catalyzed protective opening of epoxides with pivaloyl halides.

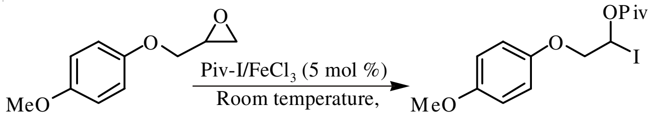
EXPERIMENTAL

All the chemicals employed in this study were procured from Sigma Aldrich. In present study, all the synthetic reactions were monitored by TLC. All the synthesized compounds were confirmed by different spectroscopic methods. The IR spectra were recorded using KBr pellets on a Perkin Elmer IR spectrophotometer. ^{1}H NMR spectra were recorded on Brucker 300 MHz Avance NMR spectrophotometer using $CdCl_3$ as solvent and TMS as internal standard (chemical shifts in δ ppm). The Mass spectra were recorded on Agilent 6300 series ion trap.

General procedure: Epoxide (0.01 mmol) is treated with pivaloyl halides (0.01 mmol) in presence of catalytic amount of Lewis acid (a-i). The reaction was stirred for 5 to 10 min and monitored the progress of the reaction by TLC.

RESULTS AND DISCUSSION

In order to find out the suitable conditions, the reaction of glycidol 4-methoxyphenyl ether with pivaloyl chloride was used as a model reaction for screening of different catalysts under solvent free conditions and the results were presented in the Table-1. All the catalysts used *i.e.* $ZnCl_2$, $FeCl_3$, $MoCl_5$, $B(C_6F_5)_3$, $SnCl_4$, TMS-OTf, $Sn(OTf)_2$, $Cu(OTf)_2$ and I_2 were found to be effective towards the protective opening of epoxides with pivaloyl halides. It was observed that glycidol 4-methoxyphenyl ether (1a) reacts with pivaloyl iodide (2a) to afford the product 3a in 99 % yield with high regio-selectivity in presence of 5 mol % of iron chloride (**Scheme-I** and **II**). Trimethyl silyl triflate, tin triflate, copper triflate gave the desired products in 60 to 70 % yields in 5 to 10 min of the time. Desired product was obtained after 12 h when the reaction



(**1a**) (**3a**)

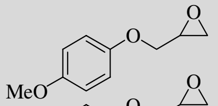
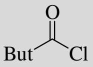
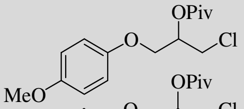
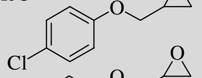
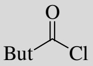
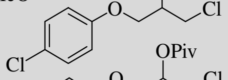
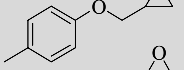
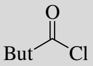
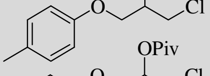
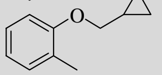
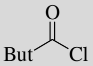
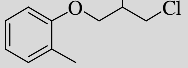
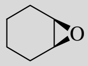
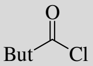
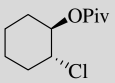
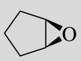
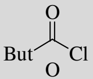
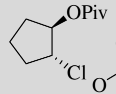
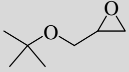
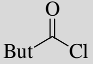
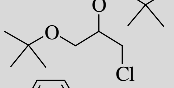
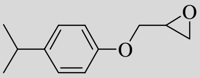
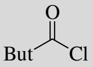
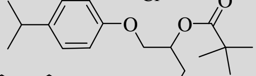
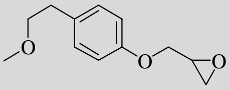
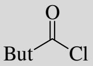
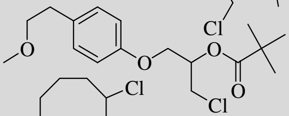
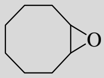
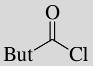
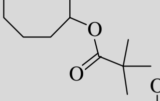
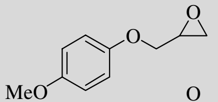
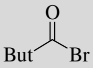
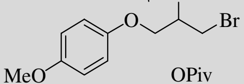
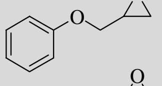
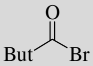
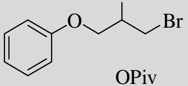
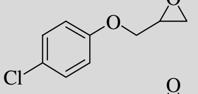
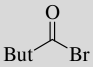
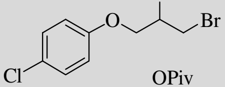
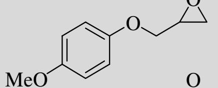
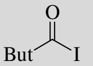
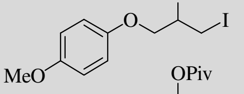
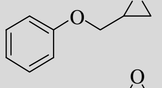
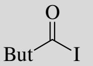
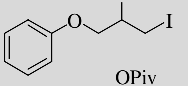
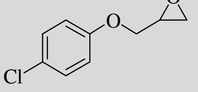
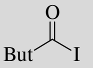
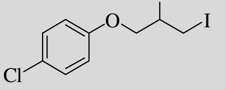
Scheme-I: Protective opening of epoxide with Piv-Cl in presence of Lewis acid catalyst-under solvent free conditions

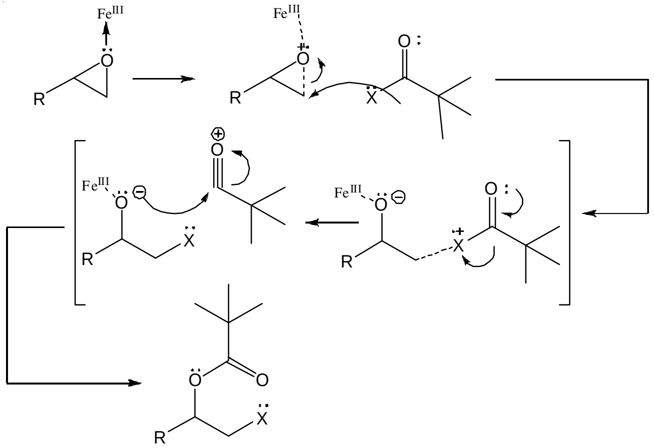
was carried out in the absence of catalyst. Although, most of these Lewis acids provided good to better yields. Iron chloride, for obvious reasons (being cheapest, milder conditions and easy to handle) was chosen for further experiments and results were mentioned in the Table-2. Epoxides from 7 to 9 were

TABLE-1
SCREENING OF LEWIS ACID CATALYSTS FOR PROTECTIVE OPENING OF EPOXIDES WITH PIVALOYL HALIDES

Entry	Lewis acid (5 mol %)	Time (min)	Yield (%)
A	$FeCl_3$	5	99
B	$SnCl_4$	5	88
C	$MoCl_5$	5	80
D	$B(C_6F_5)_3$	10	81
E	I_2	5	90
F	$ZnCl_2$	5	92
G	TMS-OTf	10	67
H	$Sn(OTf)_2$	10	65
I	$Cu(OTf)_2$	10	70
J	-	720	99

TABLE-2
LEWIS ACID CATALYZED PROTECTIVE OPENING OF EPOXIDES (POE) WITH PIVALOYL HALIDES UNDER SOLVENT FREE CONDITIONS

Entry	Substrance	Pvi-X	Product	Reaction time (min)	Yield (%)
1				5	99
2				5	96
3				10	96
4				10	95
5				10	98
6				10	97
7				5	95
8				10	94
9				5	96
10				5	95
11				5	99
12				5	99
13				5	98
14				5	99
15				5	94
16				5	96



Scheme-II: Proposed mechanism for the formation of *vic*-halo pivaloylates

were treated with pivaloyl bromides whereas the epoxides 10 to 12 were treated with pivaloyl iodide. The rate of reaction increased gradually from Cl to Br to I. In all attempts, the reactions proceeded smoothly; the epoxide ring opening appeared to be region specific. The corresponding *vic*-halo pivaloylates were obtained in excellent yields in all cases. The results were summarized in Table-2.

Conclusion

In conclusion, the present study was aimed to reduce the reaction timings from hours to minutes. An efficient protocol for protective opening of epoxide (POE) in presence of Lewis acid catalysts under solvent free conditions with shorter reaction timings was achieved.

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