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Synthesis of α-amino γ-lactone via a novel tandem three-component reaction of alkenes, glyoxylates and amines

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Abstract

α-Amino γ-lactones were generated by an $InCl_3$-mediated or $Sc(OTf)_3$-catalyzed three-component reaction of alkenes, glyoxylates and amines. © 2000 Published by Elsevier Science Ltd.

The development of new methods for the synthesis of chiral or achiral α-amino acid derivatives[1] is an important area of synthetic efforts. Glyoxylate imines provide access to non-proteinogenic α-amino acids through ene reactions,[2] cycloaddition reactions,[3] radical additions,[4] or nucleophilic additions.[5] α-Amino γ-lactones are the structural feature of a number of natural products.[6] In addition, certain functionalized γ-butyrolactones are pheromones for several insect species[7] and some are utilized as flavoring components[8] and plant-growth regulators.[9] They are also important intermediates for the synthesis of many natural products such as alkaloids, macrocycliantibiotics, liganlactones, pheromones, antileukemics, and flavor components.[10] Our interests in the synthesis of non-proteinogenic amino acids and their derivatives require a rapid access of amino lactones. Herein, we wish to report the formation of α-amino γ-lactones via an $InCl_3$-mediated three-component tandem cyclization of alkenes, glyoxylates and amines.[11]

When a mixture of 2-ethyl 1-butene and an imine, generated from *n*-butyl glyoxylate and 2,4-dichloroaniline, was stirred with indium(III) chloride in the presence of toluenesulfonic acid (1.5 equiv.) in methylene chloride at reflux, the appearance of a new spot was immediately observed by TLC within 5 min. To ensure the completion of the reaction, the stirring was continued overnight. After a usual work-up, the reaction mixture was concentrated in vacuo. The ^1H NMR spectrum of the crude reaction mixture showed the formation of the desired cyclization product. Subsequently, column chromatography of the crude material on silica gel provided the desired product, α-2,4-dichlorophenylamino-γ,γ-diethyl γ-butyrolactone, in 54% yield (Eq. (1)).

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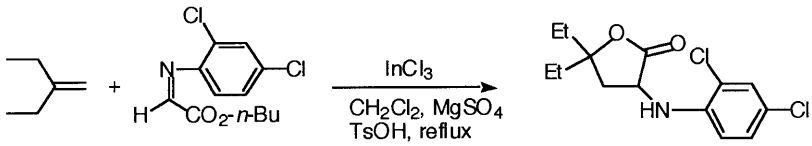
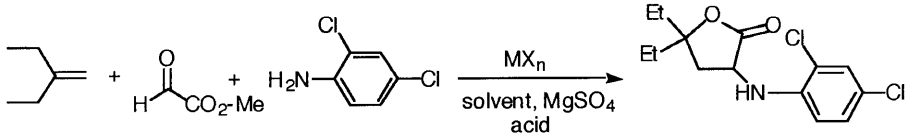


(1)

It is desirable from a synthetic point of view that the imine esters, generated in situ from glyoxylates and amines, immediately react with alkenes to afford the α-amino-γ-butyrolactones in one-pot without the need of preforming the imines. It was found that the cyclization reaction of methyl glyoxylate, 2,4-dichloroaniline and 2-ethyl 1-butene was successfully promoted by metal salts in the presence of toluenesulfonic acid (1.5 equiv.) and $MgSO_4$ under refluxing conditions (Eq. (2)). Among the metal salts screened, indium(III) chloride promoted the reaction most effectively, while the yield of the adduct was lower when other metal salts were used. No reaction was observed if only $MgSO_4$ was present. Various solvents were used in the model reaction with indium(III) chloride as a mediator; the results are summarized in Table 1. Among those tested (such as chloroform, 1,2-dichloroethane, tetrahydrofuran, and toluene), methylene chloride provided the best results. It should be mentioned that the acid played a key role in the three-component cyclization reaction. More than one equivalent of acid is necessary for the cyclization to provide practical yields. Various organic acids such as trifluoromethanesulfonic acid, trifluoroacetic acid, acetic acid, and toluenesulfonic acid were examined. Among them, toluenesulfonic acid afforded the best results.



(2)

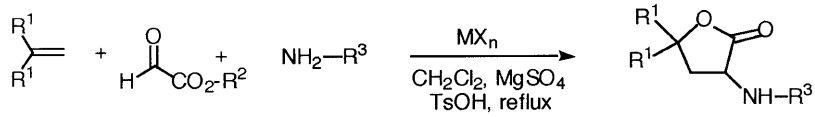
Table 1
Effect of MXn, acids and solvents on the formal [3+2] cyclization[a]

Run	MXn	Acid	Solvent	Temp.	Yield (%)
1	$InCl_3$[b]	CF_3SO_3H	CH_2Cl_2	Reflux	49
2	$InCl_3$	CF_3CO_2H	CH_2Cl_2	Reflux	68
3	$InCl_3$	CH_3CO_2H	CH_2Cl_2	Reflux	70
4	$InCl_3$	TsOH	CH_2Cl_2	Reflux	76(30)[c]
5	$InCl_3$	TsOH	CH_2Cl_2	Rt	32
6	$InCl_3$	TsOH	$CHCl_3$	Reflux	38
7	$InCl_3$	TsOH	$ClCH_2CH_2Cl$	Reflux	52
8	$YbCl_3$[d]	TsOH	CH_2Cl_2	Reflux	46
9	$Sc(OTf)_3$[e]	TsOH	CH_2Cl_2	Reflux	65

[a] A stoichiometric amount of $InCl_3$ was used.
[b] Isolated yields.
[c] A catalytic amount of $InCl_3$ (20 mol%) was used.
[d] A stoichiometric amount of $YbCl_3$ was used.
[e] A catalytic amount of $Sc(OTf)_3$ (10 mol%) was used.

The one-pot reactions of various glyoxylates, amines, and alkenes were found to be effectively promoted by indium(III) chloride in the presence of $MgSO_4$ and toluenesulfonic acid at reflux

in methylene chloride (Eq. (3)) (Table 2). The following features are noteworthy in these reactions. (1) The reactivity order of the aromatic amines is 2,4,6-trichloroaniline, 2,4-dichloroaniline>*p*-fluoroaniline>*p*-chloroaniline>aniline, indicating the importance of the electronic nature of the amines. (2) The ester groups of the glyoxylates have an observable effect on the reaction. The reactivity order follows MeO, EtO>Bu^{n}O, Pr^{i}O, which showed that the increase in steric hindrance of glyoxylates hindered the cyclization. (3) Both acyclic alkenes and cyclic alkenes such as methylenecyclopentane and methylenecyclohexane worked well for the cyclization. However, simple monosubstituted alkenes did not give the desired cyclization product. (4) A stoichiometric amount of indium(III) chloride gave a slightly better result than a catalytic amount of scandium triflate. While a very low yield of the desired cyclization product was obtained in the existence of 20 mol% of indium trichloride. (5) α-Alkyl α-aryl alkene such as α-methyl styrene provided a high yield of α-amino lactone when 2,4,6-trichloroaniline was used. However, it underwent aza-Diels–Alder reaction rather than the formal [3+2] cyclization transformation in the case of 2,4-dichloroaniline to provide tetrahydroquinoline derivative in good yield (Eq. (4)). Furthermore the ratio of the two diastereoisomers was almost 1:1. (6) *N*-tosyl protected α-amino γ-butyrolactone has also been synthesized via the mild three-component cyclization procedure in an acceptable yield, although 0.5 equiv. of reusable scandium triflate needs to be used.

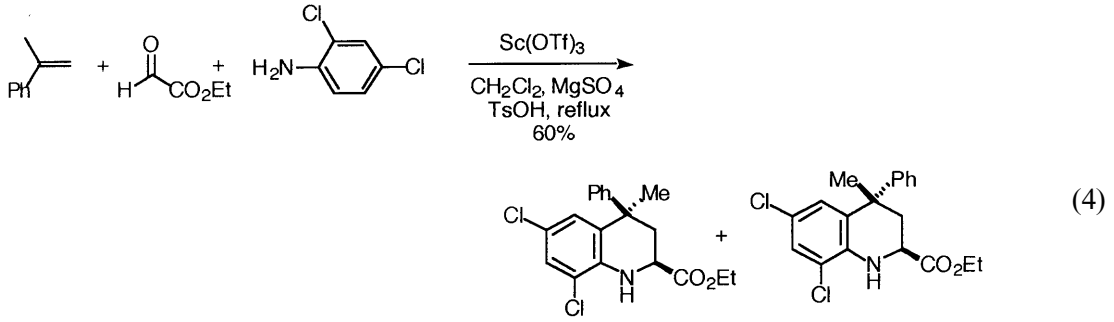


(3)

Table 2
Three-component cyclizations of alkenes, glyoxylates and amines[a]

Run	Alkene	R^2	R^3	Yield(%)[b]
1	2-Ethyl-1-butene	Me	2,4-Dichlorophenyl	76(40)[c]
2	2-Ethyl-1-butene	Et	2,4-Dichlorophenyl	68
3	2-Ethyl-1-butene	Pr^i	2,4-Dichlorophenyl	61
4	2-Ethyl-1-butene	Bu^n	2,4-Dichlorophenyl	57
5	Methylenecyclopentane	Me	2,4-Dichlorophenyl	63(49)[c]
6	Methylenecyclohexane	Me	2,4-Dichlorophenyl	61(52)[c]
7	Isobutylene	Bu^n	2,4,6-Trichlorophenyl	87
8	2-Ethyl-1-butene	Bu^n	2,4,6-Trichlorophenyl	73
9	Methylenecyclohexane	Bu^n	2,4,6-Trichlorophenyl	63
10	Methylenecyclopentane	Bu^n	2,4,6-Trichlorophenyl	53
11	Isobutylene	Bu^n	2,4,6-Trichlorophenyl	62
12	Methylenecyclopentane	Et	4-Fluorophenyl	48
13	Methylenecyclopentane	Et	4-Chlorophenyl	35
14	Methylenecyclopentane	Et	Phenyl	10
15	α-Methylstyrene	Bu^n	2,4,6-Trichlorophenyl	76[d]
16	α-Methylstyrene	Bu^n	Ts	45[e]

[a] A stoichiometric amount of $InCl_3$ (1 equiv.) was used.
[b] Isolated yields.
[c] A catalytic amount of $Sc(OTf)_3$ (10 mol%) was used.
[d] 20 mol% of $Sc(OTf)_3$ was used.
[e] 50 mol% of $Sc(OTf)_3$ was used.



(4)

In conclusion, indium (III) chloride is an efficient mediator both for the cyclization of imine esters with alkenes and for the one-pot cyclization reaction of glyoxylates, amines, and alkenes to provide α-amino γ-substituted γ-butyrolactones of biological and synthetic importance in useful yields under mild conditions. Further synthetic application of these reactions is now in progress.

General reaction procedure: To a suspension of indium(III) chloride (1 mmol) in CH_2Cl_2 were added a freshly distilled glyoxylate (1 mmol), an amine (1.1 mmol), an alkene (1.2 mmol), a toluenesulfonic acid (1.5 mmol), and $MgSO_4$ (2 mmol) successively at room temperature. After stirring at reflux overnight, a saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL) were added, and the mixture was extracted with ethyl acetate. The combined organic phase was dried over $MgSO_4$ and concentrated. The crude material was purified by silica gel chromatography to give the desired product.

Acknowledgements

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