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An improved procedure to prepare 3-methyl-4-nitroalkylenethylisoxazoles and their reaction under catalytic enantioselective Michael addition with nitromethane.

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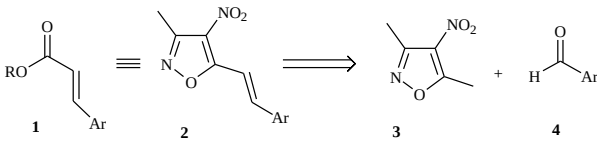
Herein, we describe a short synthesis of 3-methyl-4-nitro-5-alkylethenyl isoxazoles and their reactivity as Michael acceptor. The title compounds reacted with nitromethane under phase-transfer catalysis to provide highly enantioenriched adducts (up to 93% ee) which were then converted to the corresponding γ-nitroacids.

Introduction

The isoxazoles nucleus is an important pharmacophore in medicinal chemistry, due to its isosterism with an ester.[1] In addition isoxazoles could be employed as precursors to notable organic compounds such as 1,3-dicarbonyls,[2] hydroxyketones,[3] azirines,[4] enamines and β-hydroxynitriles.[5] In recent past, we have developed several synthetic routes starting from aromatic styrylisoxazoles 2 (Scheme 1).[6-11] In compounds **2**, the 4-nitroisoxazole core activates the exocyclic alkene to react with soft nucleophiles. The 4-nitroisoxazole could be converted to a carboxylate *via* basic,[12] oxidative[13] and acidic[14] procedures which justified the definition of compounds **2** as synthetic equivalent to cinnamates **1**.

Scheme 1. Retrosynthetic analysis of 3-methyl-4-nitro-5-styrilisoxazoles **2**

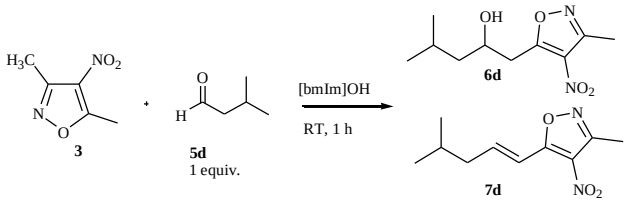


Following our reports, the synthetic relevance of compounds **2** has been recognized by other groups: Shibata reported the synthesis of trifluoromethylisoxazolines *via* addition of CF_3^- nucleophiles to compounds **2**;[15] Yuan reported a highly enantioselective thiolate addition to compounds **2** catalysed by bifunctional organocatalysts;[14] Rui Wang reported a highly enantioselective addition of unsaturated lactams to **2** catalysed by quinine-based thioureas.[16]

The preparation of aromatic compounds **2** proceeded *via* condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **3** and aromatic or heteroaromatic aldehydes **4**.[17]

However, the same procedure failed when aliphatic aldehydes were employed.[6,18] Considering the growing interest in reagents **2**, we have recently reported a method to prepare aliphatic 5-ethenyl-4-nitroisoxazoles.[18] The synthesis involved four steps and allowed obtaining compounds **7** (Scheme 2) in high yields and exclusively as *E* stereoisomer.[18]

Scheme 2. Condensation of **3** and aliphatic aldehydes in [bmIm]-OH.



Results and discussion

With the intention of streamlining the preparation of compounds **7**, we reconsidered the condensation of commercially available **3** and aliphatic aldehydes **5a-i** under a new set of hitherto unexplored conditions. This study identified a two-step procedure that allowed condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **3** and aliphatic aldehydes **5a-i** to alkylethenylisoxazole **7a-i** (Scheme 2). The synthetic relevance of compounds **7a-i** was then demonstrated by their reaction with nitromethane under phase transfer catalysis (PTC).[19] This reaction

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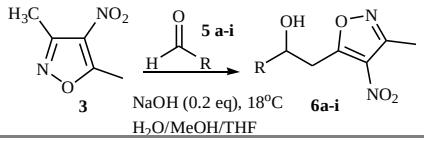
provided pharmaceutically relevant adducts **9a-i** in high enantiomeric excesses (Table 4).

Table 1. Synthesis of hydroxyl isoxazoles.

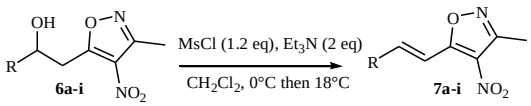


Entry[a]	Ald.	R group	T [h]	Prod.	Yields[b] [%]
1	**5a**	CH_2CH_3	36	**6a**	90
2	**5b**	$CH_2CH_2CH_3$	36	**6b**	88
3	**5c**	$(CH_2)_3CH_3$	36	**6c**	88
4	**5d**	$CH_2CH(CH_3)_2$	36	**6d**	92
5	**5e**	$(CH_2)_4CH_3$	48	**6e**	87
6	**5f**	$(CH_2)_5CH_3$	48	**6f**	88
7	**5g**	$(CH_2)_6CH_3$	48	**6g**	85
8	**5h**	$(CH_2)_7CH_3$	60	**6h**	84
9	**5i**	$(CH_2)_8CH_3$	60	**6i**	84

[a] Reaction Conditions: 3,5-dimethyl-4-nitroisoxazole **3** (5 mmol), H_2O/MeOH/THF, NaOH (0.2 mmol), aldehyde **5a-i** (6 mmol), 18ºC. [b] Isolated yields after flash column chromatography.

During our studies on the preparation of compounds **7**, Reddy reported a fast preparation of **2** (yields of 85-92% in 10-15 minutes) that occurred at room temperature. The new procedure involved the use of 1-butyl-3-methylimidazolium hydroxide [bmIm]-OH as the media.[20] The fast rates described by Reddy prompted us in reacting **3** and **5d** (Scheme 2) in [bmIm]-OH.

Table 2. Synthesis of alkenethyl isoxazoles.



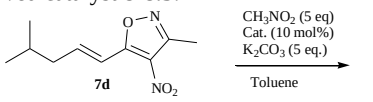
Entry	R	Prod.	Yield [%][b]
1	CH_2CH_3	**7a**[d]	98
2	$CH_2CH_2CH_3$	**7b**[d]	96
3	$(CH_2)_3CH_3$	**7c**	97
4	$CH_2CH(CH_3)_2$	**7d**	95
5	$(CH_2)_4CH_3$	**7e**	96
6	$(CH_2)_5CH_3$	**7f**	94
7	$(CH_2)_6CH_3$	**7g**	90
8	$(CH_2)_7CH_3$	**7h**	88
9	$(CH_2)_8CH_3$	**7i**	88

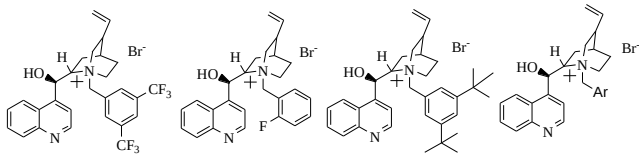
[a] Reaction Conditions: **6 a-i** (1 mmol), CH_2Cl_2 (7mL), MsCl (1.2 mmol), Et_3N (2 mmol), 0°C then 18°C. [b] Isolated yields after flash column chromatography.

Hence, equimolar amounts of 3,5-dimethyl-4-nitroisoxazole **3** and isovaleraldehyde **5d** were taken in IL [bmIm]-OH and the reaction mixture was stirred at room temperature for 1h. This reaction provided 20% of compound **7d** and 32% of alcohol **6d**. Increase of temperature, reaction time or reactant concentration did not proved useful and **7d** was obtained in yields not superior to 20-25%.

The unprecedented reaction of **3** and aliphatic **5d** in IL [bmIm]-OH was explained considering quantitative formation of deprotonated **3** which is very stable in a polar solvent. The high concentration of deprotonated **3** was then responsible for the generation of compounds **6d** and **7d**. In order to prove this, we have designed a new protocol in which compound **3** was first reacted with 1 equiv of NaOH in a mixture of 9 : 1 of ethanol : water and then the resulting metallated-**3** quenched with isovaleraldehyde **5d**.

Table 3. Representative results of the screening of cinchonidine-derived catalyst **8**-**8.5**.





Entry[a]	Cat.	Temp [°C]	T [h]	Conv. [%][b]	ee. [%][c]
1	**8**	RT	1.5	98	86
2	**8**	0	3	98	87(72)[d]
3	**8**	-30	18	87	82
4	**8.1**	0	18	98	73
5	**8.2**	RT	0.25	92	86
6	**8.2**	0	1.5	92	86(85)[d]
7	**8.3**	0	18	98	74
8	**8.4**	0	48	98	78
9	**8.5**	0	24	98	53

[a] Reaction Conditions: alkenethylisoxazole **7d** (0.1 mmol), toluene (1.0 mL), cat. **8**-**8.5** (10 mol%), nitromethane (0.5 mmol), K_2CO_3 (0.5 mmol). [b] Conversion was determined by ^1H NMR analysis. [c] The enantiomeric excess (*ee*) of the product was determined by chiral stationary phase HPLC. [d] in parentheses the *ee* of *ent*-**9d** obtained using the pseudoenantiomeric catalysts **8** and **8.2**.

This new protocol provided about 50% of compounds **6d** and **7d** in 1 : 1 ratio, proving therefore that the amount of ionized **3** was crucial to ensure progress of the desired aldol reaction.

Further improvements were logically achieved by *(a)* reduction of NaOH base to 0.2 equiv, to decrease aldehyde self-condensation; *(b)* replacement of ethanol with methanol to increase the amount of isoxazole **3** in solution; *(c)* addition of THF as a co-solvent to favor the formation of homogeneous phase.

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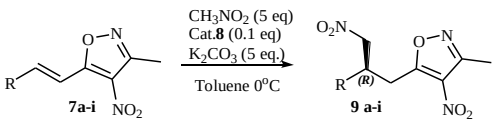
Delightfully, under this set of optimized conditions, the reaction of **3** and aldehydes **5a-i** proceeded to completion and alcohols **6a-i** were obtained in high isolated yields (Table 1).

Compounds **6a-i** were then treated with a small excess of methane sulfonyl chloride (1.2 equiv) and an excess of triethylamine (2 equiv), providing correspondent alkenes **7a-i** in good to excellent yields (Table 2). Significantly, only the *E*-alkene was observed.

This two steps procedure run under a milder set of condition (NaOH in H_2O/MeOH) compared to those previously reported (LDA in THF)[18] and expanded significantly the scope of alkenes **7** that could be prepared. The reactivity of compounds **7a-i** was then tested in the Michael reaction with nitromethane. We initially treated a solution of **7d** in toluene (0.1M) with nitromethane (5 equiv), solid K_2CO_3 (5 equiv), a suitable combination of base and solvent already reported by us,[6] with a range of *cinchonidine*-derived phase transfer catalysts (Table 3).

The use of catalyst **8** and **8.2** at room temperature provided compound **9d** in 86% *ee* (Table 3, entries 1 and 5). The reaction carried out at lower temperature (-30°C) furnished **9d** in a decreased enantiomeric excess (Table 3, entry 3). The use of commercially available catalyst **8.3** provided desired product **9d** in a lower 74% at 0°C (Table 3, entry 7). Similarly, catalysts **8.4** and **8.5** gave **9d** in reduced enantioselectivity (Table 3, entries 8 and 9). Final optimisation involved the use of 10 mol% of catalyst and diluting the reaction from 0.1 M to 0.03M, which enhanced the *ee*. Hence, the optimised set of conditions required the use of 10 mol% of catalyst **8** at 0°C, solid K_2CO_3 as the base, a concentration of reagents of 0.03M (Table 3, entry 4). Importantly, the use of pseudoenantiomeric catalysts allowed obtaining *ent*-**9d** in similarly high ee (Table 3, entries 2 and 6).

Table 4. Enantioselective addition of nitromethane to alkenethenylisoxazole **7a-i** under the catalysis of **8**.



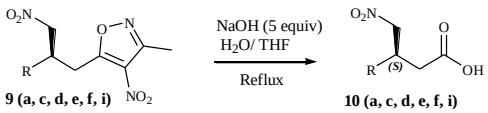
Entry[a]	R	Prod.	Yield [%][b]	ee [%][c]
1	CH_2CH_3	**9a**[d]	91	93
2	$CH_2CH_2CH_3$	**9b**[d]	91	87
3	$(CH_2)_3CH_3$	**9c**	90	88
4	$CH_2CH(CH_3)_2$	**9d**[d]	90	89
5	$(CH_2)_4CH_3$	**9e**[d]	91	88
6	$(CH_2)_5CH_3$	**9f**[d]	90	86
7	$(CH_2)_6CH_3$	**9g**	99	83
8	$(CH_2)_7CH_3$	**9h**	89	87
9	$(CH_2)_8CH_3$	**9i**[d]	89	85

[a] Reaction Condition: styrylisoxazole **7a-i** (0.2 mmol), toluene (6.7 mL), cat. **8** (0.02 mmol), CH_3NO_2 (1 mmol), K_2CO_3 (1 mmol). [b] Isolated yields after flash column chromatography. [c] The enantiomeric excess (ee) of the product was determined by chiral stationary phase HPLC. [d] Reaction performed on a 5.0 mmol scale.

The scope of the reaction was shown by reacting alkylethenylisoxazoles **7 a-i** with nitromethane under the catalysis of **8** (Table 4). The results collected pointed out: *(a)* compounds containing either short (**7a**, **7b**) or long chain (**7h**, **7i**) were equally good substrates and correspondent **9a,b** and **9h,i** were obtained in good yields and in ee up to 93% *ee*; *(b)* importantly, it was verified that at least compounds **9a**,**c**,**d**,**e**,**f**,**i** could be obtained in a preparative scale (Table 4) without loss of yield or enantioselectivity. The absolute configuration of compounds **9a-i** obtained was determined to be *R* by comparison of optical rotation and HPLC data of compounds **10d** and *ent*-**10d** with published data.[21]

The carboxylic acid functionality was then unveiled from Michael adducts **9a**,**b**,**d**,**e**,**f**,**i** (Table 5) which were efficiently converted in to the corresponding γ-nitro acids **10a**,**b**,**d**,**e**,**f**,**i** in high yields (87%-94%).

Table 5. Synthesis of aliphatic γ-nitro acids.

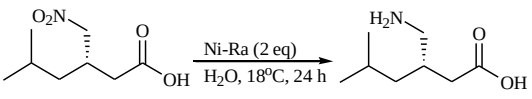


Entry	R	Prod.	Yield [%][b]
1	CH_2CH_3	**10a**[d]	92
2	$(CH_2)_3CH_3$	**10c**[d]	90
3	$CH_2CH(CH_3)_2$	**10d**	94
4	$(CH_2)_4CH_3$	**10e**	88
5	$(CH_2)_5CH_3$	**10f**	87
6	$(CH_2)_8CH_3$	**10i**	87

[a] Reaction Conditions: compounds **9** (0.25 mmol), THF (0.5 mL), aqueous NaOH (1.25 mmol), reflux. [b] Isolated yields after flash column chromatography.

This transformation required treatment with 1M aqueous NaOH in THF. The ee reflected the values of the starting materials thus demonstrating the stereochemical stability of compounds under the conditions adopted.[6] The γ-nitroacids obtained are important intermediates as precursors of γ-amino acids.[5,7,16] This has been demonstrated by reducing γ-nitroacid *ent*-**10d** to enantioenriched (S)-Pregabalin **11** (Scheme 3), using a literature procedure.[22]

Scheme 3. Preparation of enantioenriched (*S*)-Pregabalin **11**



Conclusions

In conclusions, we have developed a new short synthesis of *E*-alkenylethyl isoxazoles, the aliphatic version of a popular class of Michael acceptors. Similarly to their aromatic analogues **2**, compounds **7** reacted promptly under phase transfer catalysis providing highly enantioenriched nitromethane adducts. This study

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delivers to the scientific community a novel enantioselective strategy for the synthesis of aliphatic γ-nitroacids and confirms 4-nitro-5-alkethenylisoxazoles as useful synthon for organic synthesis.

Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and spectra of new compounds. This material is available free of charge via the Internet. See DOI: 10.1039/b000000x/

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