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A New Synthetic Approach to 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (Tic) Derivatives Via a [2 + 2 + 2] Cycloaddition Reaction

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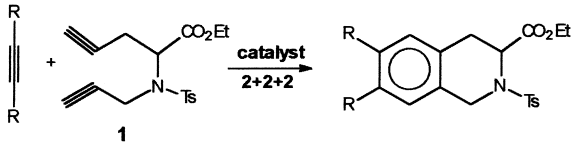
Abstract—Tetrahydroisoquinoline-3-carboxylic acid derivatives are prepared via a [2 + 2 + 2] cycloaddition reaction as a key step using Wilkinson's and $CpCo(CO)_2$ catalysts.

Tetrahydroisoquinoline (THIQ) is a rather celebrated unit and much effort has been spent in the literature because of its importance as a structural component in many biologically active natural products.[1] In addition, various derivatives of THIQ show promising biological activity. While designing conformationally restricted peptides, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) has been utilized as a restricted analogue of phenylalanine. Tic moiety was also used as a synthon for the preparation of biologically active peptides and enzyme inhibitors.[2] Incorporation of Tic in δ opioid receptors enhances δ receptor binding affinity and selectivity.[3]

The traditional methods[4] such as Bischler-Napieralski, Picter-Spengler among others[5] for Tic preparation can deliver a limited degree of functionality in the aryl ring and the substitution pattern is set prior to the cyclization step. A method that would generate the Tic ring system via a cycloaddition approach would provide a unique opportunity for the introduction of various substituents by judicious choice of the reacting partners. The currently available approaches to THIQ unit cannot easily be extended to the synthesis of Tic derivatives.[6] In essence, preparation of Tic derivatives impose more constraints in the design of synthetic strategy. In this communication we report a general method involving a [2 + 2 + 2]-cycloaddition reaction as a key step for the construction of various Tic derivatives (eq 1).



1 (1)

Preparation of the key building block **1** starts with *N*-(diphenylmethelene)glycine ethyl ester **2**.[7] Propargylation of **2** (Scheme 1) in presence of K_2CO_3/acetonitrile reflux gave **3** (86% yield). Compound **3** was hydrolyzed with dilute HCl and the resulting amino ester was protected as *N*-tosyl derivative to give **4** (mp 48–49 °C, 78% yield). The structure of **4** is well established by ^1H NMR and ^{13}C NMR spectral data ($CDCl_3$, 75.0 MHz: δ 169.3, 143.2, 137.3, 129.5, 127.2, 77.6, 72.2, 61.9, 54.0, 24.0, 21.5, 14.0). Sequential reaction of **4** with propargyl bromide and 3-bromo-1-(trimethylsilyl)-1-propyne in presence of K_2CO_3 in acetonitrile gave **1** (99%) and **5** (98%) isolated yields respectively.

Having prepared the building blocks **1** and **5** we then examined [2 + 2 + 2]-cycloaddition of diyne **1** with various acetylenic moieties using Wilkinson's catalyst (WC) (Table 1 entry no 1–5).[8] Co-trimerization reaction under WC conditions were performed using excess amount (5 equiv) of monoyne. The reaction of diyne building block **1** with propargyl alcohol smoothly proceeded to give an inseparable mixture of Tic derivatives (1:1) the regioisomers of the hydroxy methyl group on the aromatic ring. Similarly with phenylacetylene, and propyne-4-ol gave inseparable mixture of regioisomers. Later on, efforts were focused on the co-trimerization reaction of diyne **5**. The reaction of diyne **5** with butyne 1–4 diol and dimethyl acetylenedicarboxylate (DMAD) in presence of WC conditions were unsuccessful.

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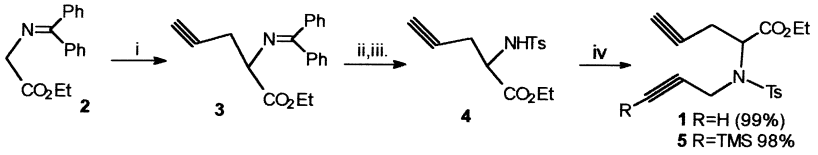
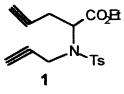
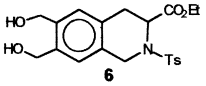
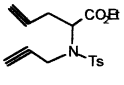
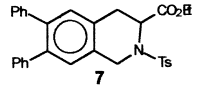
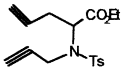
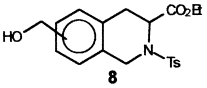
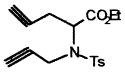
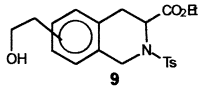
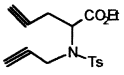
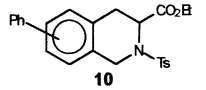
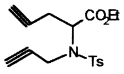
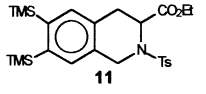
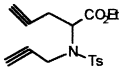
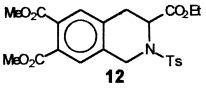
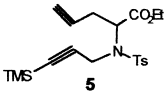
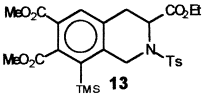
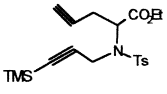
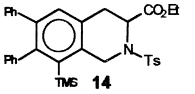
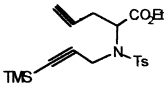
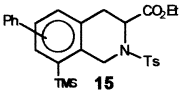


Scheme 1. (i) K_2CO_3 propargyl bromide, CH_3CN 86%; (ii) 1N HCl ether, 80%; (iii) Et_3N, TsCl, CH_2Cl_2, RT, 78%; (iv) $BrCH_2C \equiv CTMS$ K_2CO_3 CH_3CN.

Table 1.

Entry No	Diyne building block	Monoyne	Product	Catalyst	Yield (%)
1	 1		 6	$(PPh_3)_3RhCl$	53
2			 7	$(PPh_3)_3RhCl$ $CpCo(CO)_2$	15 30
3			 8	$(PPh_3)_3RhCl$	60
4			 9	$(PPh_3)_3RhCl$	65
5			 10	$(PPh_3)_3RhCl$ $CpCo(CO)_2$	30 40
6			 11	$CpCo(CO)_2$	20
7			 12	$CpCo(CO)_2$	19
8	 5		 13	$CpCo(CO)_2$	45
9			 14	$CpCo(CO)_2$	42
10			 15	$CpCo(CO)_2$	40

Alternatively co-trimerization of diyne **5** with various monoynes was explored with other catalyst conditions (e.g., $[CpCo(CO)_2]$).[9] In particular, this catalyst found to be extremely useful when the alkynes containing trimethylsilyl groups are present in any of the reacting partners. While using $CpCo(CO)_2$ conditions the cycloaddition reaction was performed using syringe pump technique. On completion of the cycloaddition reaction (TLC monitoring) co-trimerized products were isolated by flash chromatography. Various substrates

that have undergone [2 + 2 + 2] cycloaddition reaction to generate Tic derivatives are shown in Table 1. Some of the Tic derivatives prepared here deserves a special comment. Trimethylsilyl substituted Tic derivatives (**11**, **13**, **14** and **15**) can be used as a building blocks to introduce various electrophiles ipso to the TMS group.[10] Dihydroxy compound **6** is a potential precursor for the generation of Tic-based *o*-xylylene derivative.[11]

In conclusion, we have developed a general strategy for the synthesis of multifunctional Tic derivatives using transition metal catalyzed [2 + 2 + 2] cycloaddition reaction as a key step. Given the dearth of Tic derivatives, this methodology may find useful applications in bioorganic and medicinal chemistry.

General procedure for a [2 + 2 + 2] cycloaddition reaction using $CpCo(CO)_2$ conditions

To a refluxing solution of diyne building block (0.1 mmol) containing $CpCo(CO)_2$ (0.3 μL) was added a solution of monoyne containing $CpCo(CO)_2$ in toluene/octane under nitrogen atmosphere over a period of 6–10 h (syringe pump). The reaction flask was connected to vacuum distillation set up and all the volatiles were distilled off to give the crude product. The dark oily residue was chromatographed on a silica gel column by eluting with pet ether and ethyl acetate mixture to give cotrimerized product.

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References and Notes

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11. Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Pro. Int.* **1991**, *23,* 237. ^{13}C NMR data for selected compounds: (**1**) δ 13.8, 20.7, 21.4, 34.3, 58.0, 61.7, 71.5, 73.0, 78.3, 78.9, 127.7, 129.3, 136.7, 143.7, 169.0. (**5**) δ 0.03, 14.3, 21.1, 21.9, 35.8, 58.7, 62.1, 71.7, 79.7, 99.3, 100.2, 128.3, 129.7, 137.6, 143.9, 169.4. (**6**) δ 13.7, 21.5, 31.5, 44.0, 53.5, 61.3, 63.5, 127.2, 127.3, 129.5, 129.9, 130.3, 130.6, 135.9, 137.9, 143.6, 170.1. (**7**) δ 13.8, 21.5, 31.7, 44.1, 53.8, 61.3, 126.5, 127.4, 127.8, 128.1, 129.5, 129.7, 130.8, 139.1, 140.8, 143.5, 170.2. (**11**) δ 1.9, 14.0, 21.5, 31.9, 44.2, 53.7, 61.1, 127.4, 129.4, 130.1, 130.9, 133.0, 135.7, 136.5, 143.2, 144.1, 170.1. (**12**) δ 14.0, 21.6, 31.9, 44.1, 52.5, 53.0, 61.2, 127.1, 127.5, 129.5, 130.5, 130.6, 134.3, 134.9, 136.2, 143.4, 167.0, 169.2, 169.4.