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DIVERSITY-ORIENTED APPROACH TO 1,2,3,4-TETRAHYDROISO-QUINOLINE-3-CARBOXYLIC ACID (TIC) DERIVATIVES USING DIETHYL ACETAMIDOMALONATE AS A GLYCINE EQUIVALENT : FURTHER EXPANSION BY SUZUKI–MIYAURA CROSS-COUPLING REACTION†

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Abstract – Synthesis of diverse 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives and its higher analogues are reported using diethyl acetamidomalonate as a glycine equivalent. In addition, various substituted Tic derivatives are assembled by application of Suzuki–Miyaura cross-coupling reaction as a key step.

Constrained α-amino acid (AAA) derivatives play a critical role in the design of biologically active peptides and peptidomimetics.[1] 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is considered as a constrained analogue of phenylalanine (Phe), where its dihedral angle is limited to a small range (χ = +60°, -60°).[2] In addition, Tic has also been employed as a useful building block for the synthesis of various biologically active alkaloid derivatives.[3] Peptides containing Tic are also used as δ-opioid receptor antagonists.[4] Interestingly, the Tic residue adopts different conformations depending on whether it is incorporated at the *N*-terminus or at a central location of the peptide chain. Recent studies indicate that by incorporation of Tic residues, the resulting peptide can adopt both helical and β-bonded structures. Generally, Tic derivatives are assembled by Pictet–Spengler or Bischler–Napieralski reactions as a key step.[5] In order to expand the synthetic routes to Tic derivatives, development of other approaches is desirable.[6] In connection with the studies related to the bioactive conformation of peptide

† This paper is dedicated to Emeritus Professor Akira Suzuki on the occasion of his 80th birthday

ligands, various Tic derivatives were assembled (Figure 1).[7] In continuation of our efforts to design various Tic derivatives by a building block approach,[11] we conceived a general strategy to several Tic derivatives involving diethyl acetamidomalonate (DEAM) as a glycine equivalent. Although DEAM is used for the construction of various unusual amino acid derivatives, its utility towards the preparation of Tic derivatives however is less explored.[12]

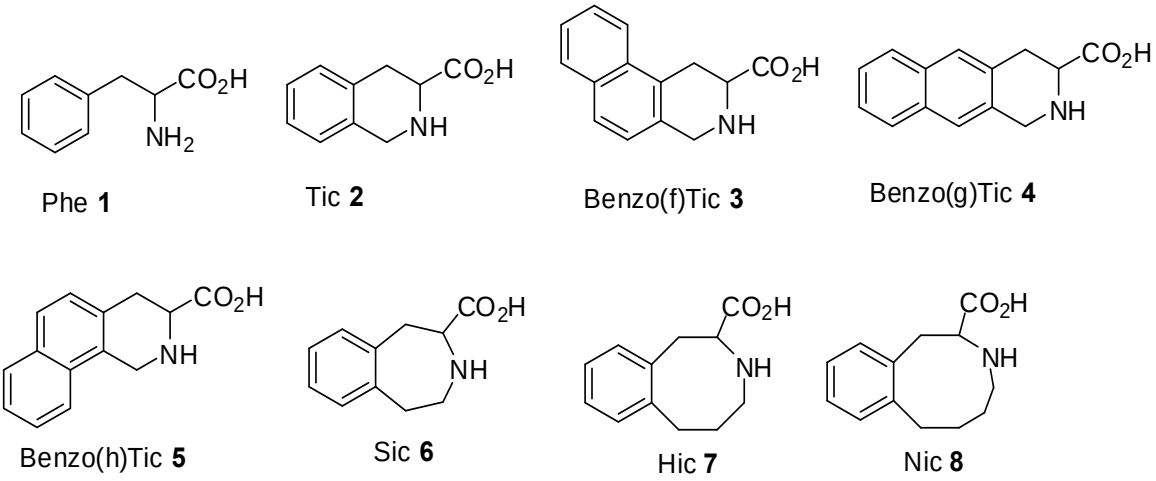
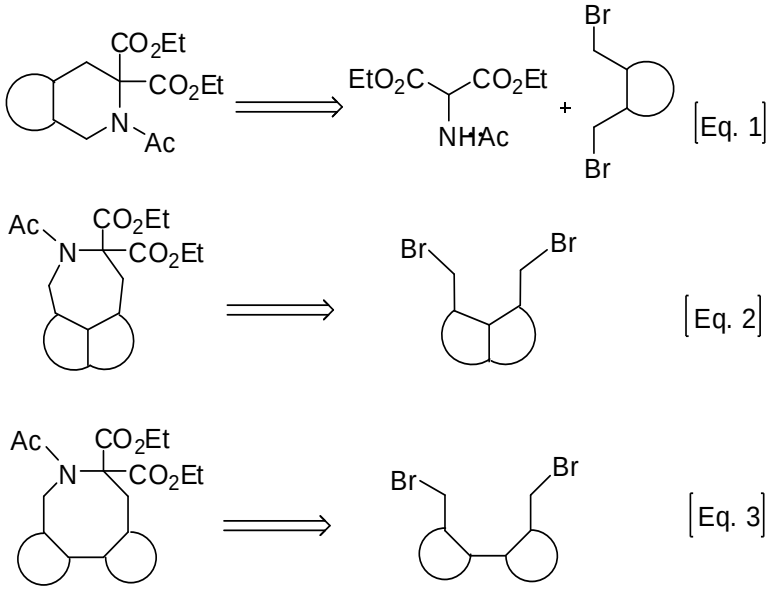


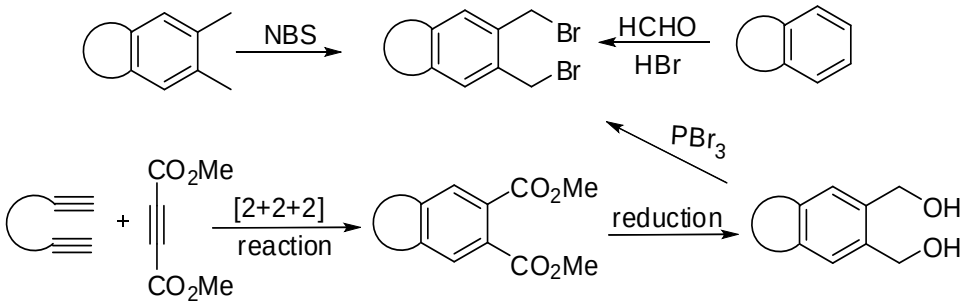
Figure 1. Various constrained AAA derivatives related to Tic

Here we describe the synthesis of various Tic derivatives, by treating α,α'-dibromo-*o*-xylenes, with DEAM in presence of a mild base such as K_2CO_3 (Scheme 1). By choosing an appropriate dibromo derivative one can prepare Tic and its higher analogues (Eq. 1 – Eq. 3).



Scheme 1. Retrosynthetic approach to Tic and its higher analogues

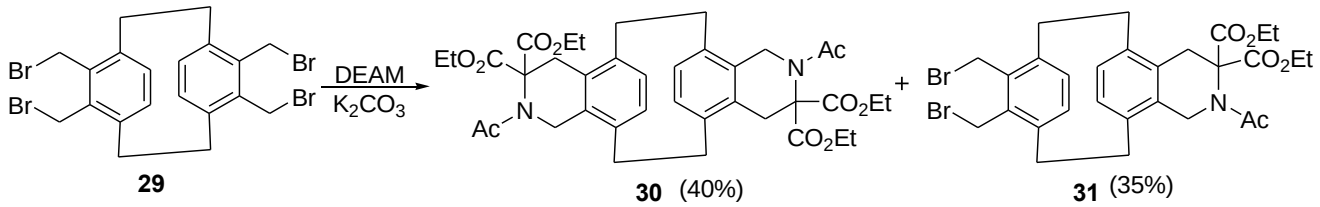
The required dibromo derivatives can be obtained from the corresponding dimethyl aromatic compounds with the aid of benzylic bromination using *N*-bromosuccinimide (NBS)[13] under free radical condition or by bromination of the corresponding diols with PBr_3 (Scheme 2).[14] The required diols were assembled by a [2+2+2]cycloaddition reaction and reduction as key steps.[15] Alternatively, a bromomethylation[16] strategy can also be adopted for this purpose.



Scheme 2. Synthetic approaches to α,α'-dibromo-*o*-xylene derivatives

Reaction of α,α'-dibromo-*o*-xylene derivatives (Table 1) with DEAM in presence of K_2CO_3 gave various Tic derivatives in moderate yields. In a typical experimental procedure, a solution of dibromide (1 equivalent) in dry acetonitrile was treated with DEAM (1.1 equivalent), powdered potassium carbonate (6 equivalents) and tetrabutylammonium hydrogen sulfate (0.2 equivalent) as a phase-transfer catalyst. At the conclusion of the reaction (TLC monitoring), the reaction mixture was passed through a small pad of celite. The filtrate was concentrated and extracted with ethyl acetate (3 × 25 mL). The crude product obtained was purified by silica-gel column chromatography. Elution of the column with ethyl acetate-petroleum ether mixture furnished the required Tic derivative.

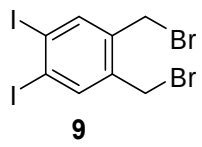
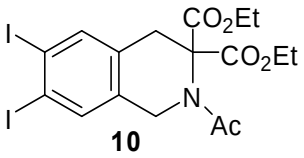
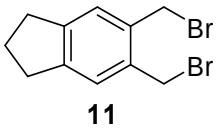
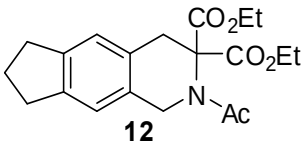
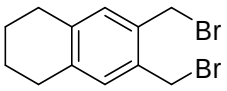
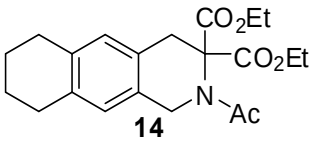
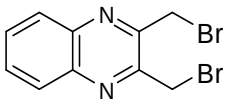
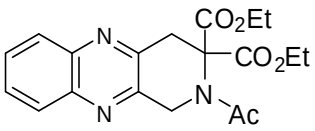
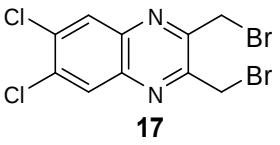
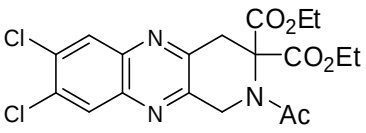
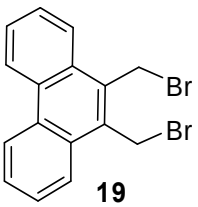
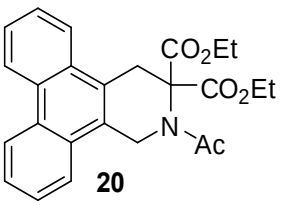
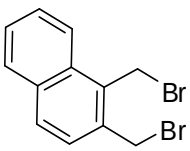
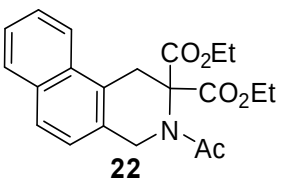
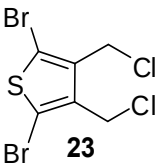
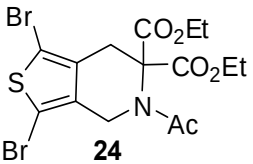
This methodology was also extended for the synthesis of higher analogues of Tic. Towards the preparation of Sic derivative **26,** the required dibromide was prepared from the corresponding anhydride.[17] Later, treatment of the dibromide **25** with DEAM in the presence of K_2CO_3 gave Sic derivative **26**. Along similar lines, Hic derivative **28** was assembled starting with the commercially available 2,2′-bis(bromomethyl)-1,1′-biphenyl **27** (Table 2).



29 **30** (40%) **31** (35%)

Scheme 3. Cyclophane based Tic derivative

Table 1. Preparation of various Tic derivatives

entry	starting material	product	condition	yield (%)
1	 **9**	 **10**	A	41
2	 **11**	 **12**	B	42
3	 **13**	 **14**	B	42
4	 **15**	 **16**	B	75
5	 **17**	 **18**	B	72
6	 **19**	 **20**	A	45
7	 **21**	 **22**	B	48
8	 **23**	 **24**	B	56

[a]Conditions A: DEAM (1 equiv.), K_2CO_3 (5 equiv.), MeCN reflux, 24 h.

Conditions B: DEAM (1.1 equiv.), K_2CO_3 (6 equiv.), TBAHS (0.2 equiv.), MeCN reflux, 20-22 h.

Table 2. Preparation of Sic and Hic derivatives

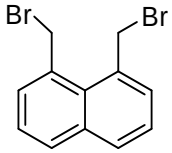
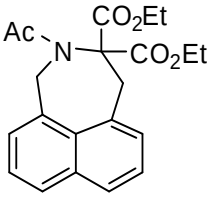
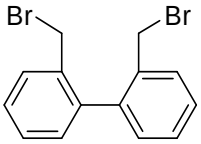
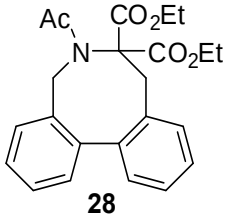
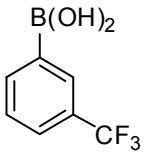
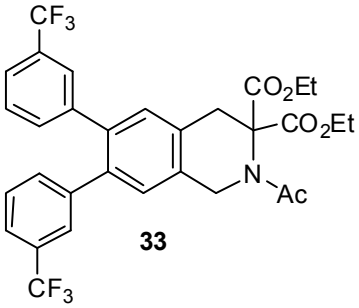
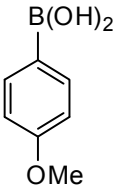
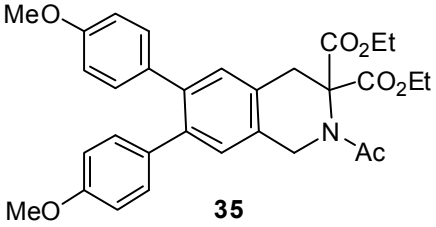
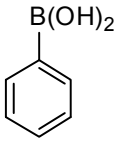
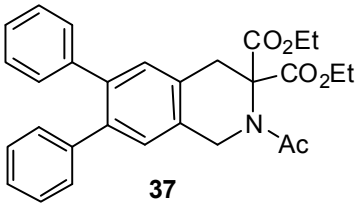
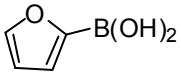
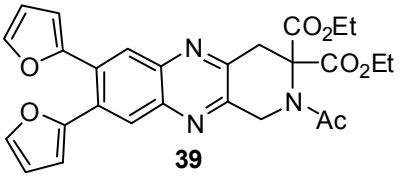
entry	starting material	product	condition[a]	yield (%)
1	 **25**	 **26**	A	64
2	 **27**	 **28**	A	64

Table 3. Expansion of Tic derivatives by Suzuki cross-coupling reaction

entry	substrate	boronic acid	product	condition[a]	yield (%)
1	**10**	 **32**	 **33**	A	35
2	**10**	 **34**	 **35**	A	49
3	**10**	 **36**	 **37**	A	30
4	**18**	 **38**	 **39**	B	37

[a]Conditions A: $[Pd_2(dba)_3]$, Buchwald Ligand (5 mol%), Na_2CO_3, THF/toluene/H_2O, 70 °C.

Conditions B: $[Pd_2(dba)_3]$, $LiCO_3$, dioxane:H_2O (3:1), MW, 5 min.

It is interesting to note that this strategy could also be extended to cyclophane derivative **29**. Accordingly, when tetrabromide **29**[18] was reacted with DEAM under the above condition to give di-Tic derivative **30** along with mono-Tic derivative **31** in 40% and 35% yields, respectively. The regiochemistry of compound **30** has been established by single crystal X-ray diffraction analysis.[19] In view of various recent applications of [2.2] paracyclophane chemistry these results may found useful application in bioorganic chemistry.[20]

Having prepared various Tic derivatives and its higher analogues, diiodo Tic derivative **10** was chosen as a suitable precursor to realize the Suzuki–Miyaura (SM) cross-coupling step. We found that the corresponding tetrabromo derivative is not a friendly precursor. To this end, we prepared various SM cross-coupling products by reaction of **10** with various boronic acids under Pd catalyst conditions. Several derivatives prepared by SM coupling reaction are included in Table 3.

In a typical reaction procedure, the diiodo Tic derivative **10** was reacted with an appropriate boronic acid, THF/toluene/H_2O (1:1:1) in presence of Na_2CO_3, at 70 ^oC for 15-20 min followed by addition of [$Pd_2(dba)_3$] (1.5 mol%) and Buchwald ligand[21] (5 mol%) (condition A). At the end of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude product obtained was purified by silica-gel column chromatography. Elution of the column with an ethyl acetate-petroleum ether mixture gave the cross-coupling product. In some cases, the SM cross-coupling reaction was also carried out in the absence of a ligand by using [$Pd_2(dba)_3$] (1.5 mol%), dioxane:H_2O = 3:1) in the presence of $LiCO_3$ under microwave irradiation (condition B). All new compounds were characterized on the basis of high resolution ^1H NMR and mass spectral data.

In conclusion, we have shown that DEAM is a useful glycine equivalent to prepare diverse Tic derivatives under mild reaction conditions. Further, we have shown that SM cross-coupling reaction is useful to generate various functionalized Tic derivatives. Since a large number (>900) of boronic acids are commercially available, the present strategy can be easily extended to generate a library of Tic derivatives by applying SM cross-coupling reaction. Since the development of new synthetic methods for the preparation of unusual AAA derivatives is important for designing peptide-based drugs, our methodology may be of interest to medicinal and bioorganic chemists.

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