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Synthesis of *cis* and *trans* 4-Amido 2-Carboxytetrahydroquinolines, High Affinity Ligands at the Glycine site of the NMDA Receptor

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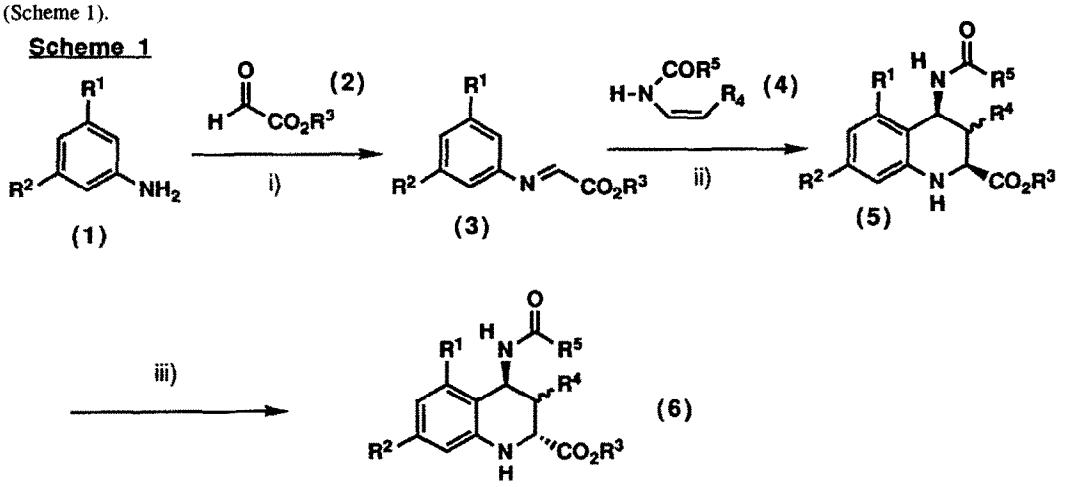
SUMMARY: N-Arylimino esters (3) react with enamides (4) under Lewis acid catalysis to afford cis 4-amido-2-carboxytetrahydroquinolines (5). The products of this reaction are easily converted to the biologically active trans conformers. Introduction of substituents at C-3 has no effect on affinity at the Glycine site of the NMDA receptor.

Following the identification of specific *trans* 4-amido 2-carboxytetrahydroquinolines as compounds with significant biological activity,[1] an efficient synthesis of this ring system was required. Previous procedures[2] required several steps and allowed access only to limited substitution of the tetrahydroquinoline nucleus with the 2,4- *trans* configuration.

N-Aryl imines are known to act as 2-azadienes undergoing Lewis acid catalysed reactions with electron rich dienophiles to form the tetrahydroquinoline ring system.[3-7] We now wish to report a significant variation of this reaction in which anilines (**1**) are converted into the desired 2-carboxy-4-amido tetrahydroquinolines (**5**) in two steps (Scheme 1).

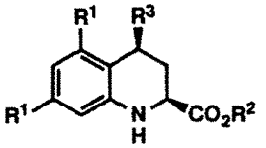
Scheme 1



Reagents: i) Na_2SO_4, CH_2Cl_2 ; ii) $BF_3.Et_2O$; iii) NaOMe, MeOH

Treatment of the aniline (**1**) with a suitable glyoxalate ester (**2**) using dry Na_2SO_4 in CH_2Cl_2 affords the N-arylimino ester (**3**) in good yield (70-90%). These intermediates are unstable and are best used *in situ*, simply by filtration of the dehydrating agent to afford a solution of the N - arylimino ester.[7] The enamide (**4**) is then added to this solution followed by a catalytic quantity (10%) of $BF_3.Et_2O$. The cyclisations are complete within one hour at room temperature to give the 2-carboxy-4-amido tetrahydroquinolines in 40-60% yield. Table 1 shows the variety of tetrahydroquinolines that were made using this method.

Table 1: 2 - Carboxy - 4 - Amidotetrahydroquinolines

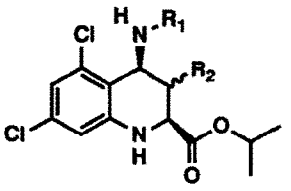


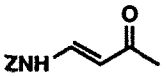
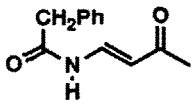
Enamide	R^1	R^2	R^3	%Yield	*cis : trans*	No
 (7)	Cl	Me	NHZ	30-50	20:1	(8)
	Cl	^{i}Pr	NHZ	40-50	20:1	(9)
	Br	Me	NHZ	60	5:1	(10)
	Br	^{i}Pr	NHZ	47	20:1	(11)

The initial studies were carried out using N-vinylbenzyloxycarbamate (**7**)[8] as the enamide, to provide the 4-amino derivative in a form suitable for further manipulation. Using this enamide resulted in predominant formation of the 2,4-*cis* conformers (**8** - **11**). Variations of aromatic substitution had little effect on either chemical yield or the *cis:trans* ratio. The product mixture was easily epimerised to give predominantly the *trans* conformer (**6**) by treatment with NaOMe (5%) in methanol (Scheme 1).

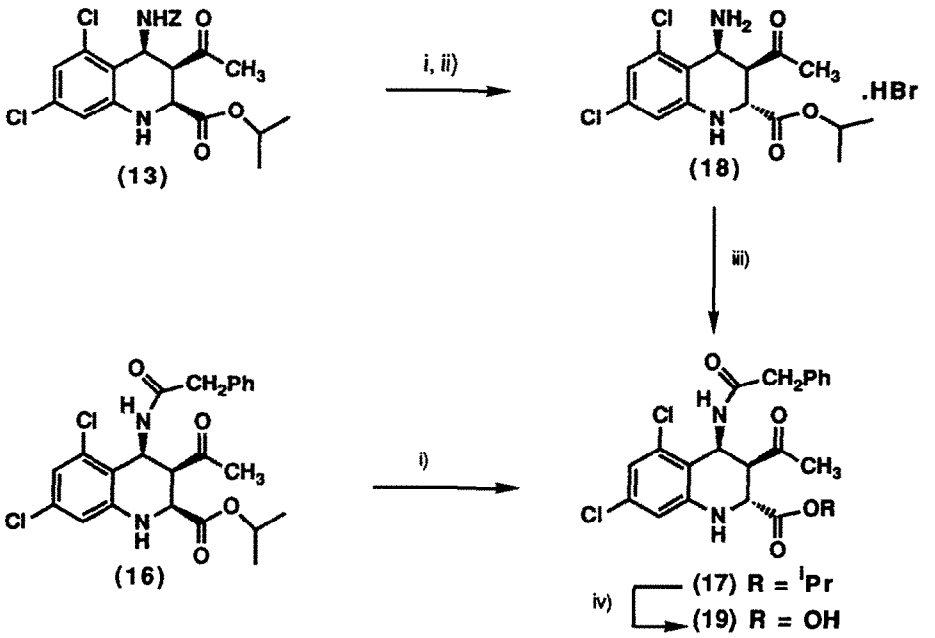
Substituted enamides were used to introduce functionality at C-3 of the product tetrahydroquinoline (Table 2). The electron deficient α,β-unsaturated enamide (**12**) gave the 3-acetyl derivatives (**13**) and (**14**) the reaction proceeding smoothly with the same 2,4-regioselectivity and stereoselectivity. High field n.m.r. studies showed that the major products in this reaction was the 2,3,4 - *cis* stereoisomer. The only isolable product from the reaction of (**15**) was the 2,3,4 - *cis* isomer (**16**) in low yield. Treatment of (**16**) with NaOMe (5%) in methanol at room temperature resulted in epimerisation to (**17**). This result was confirmed by an independent synthesis of (**17**) from (**13**). Epimerisation of (**13**) followed by deprotection using HBr/AcOH afforded (**18**), which was subsequently acylated to give (**17**) (Scheme 2).

Table 2 : 3 - Substituted 2 - Carboxy - 4 - Amidotetrahydroquinolines



Enamide	R^1	R^2	◀R^2	No	····R^2	No
 (12)	Z	$COCH_3$	30%	(13)	10%	(14)
 (15)	$COCH_2Ph$	$COCH_3$	15%	(16)	-	-

Scheme 2



Reagents : i) NaOMe, MeOH; ii) HBr, AcOH; iii) $PhCO_2H$, DCC, HOBt; iv) LiOH.

The C-3 acetyl compound (**19**) had the same affinity for the glycine site of the NMDA receptor as the 3-unsubstituted derivative.[1,9,10] This observation is consistant with the proposal,[1,9,10] that the 2-equatorial 4-axial conformer is bound to the receptor.[1] In addition no loss of affinity was also observed when 5,7 dichloro was replaced by 5,7 dibromo.

In conclusion, N-arylimino esters react readily with an enamide under Lewis acid catalysis to afford cis 2-carboxy-4-amido carboxytetrahydroquinolines in good yield. The isolated products are easily epimerised to give the biologically active *trans* stereoisomers. Introduction of a C-3 substituent has no effect an affinity, indicating a possible site for further exploration in this series. The methodology therefore allows regio- and stereoselective access to all substituted derivatives of the tetrahydroquinoline nucleus.

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