Synthesis of Tacrine Derivatives Under Solventless Conditions

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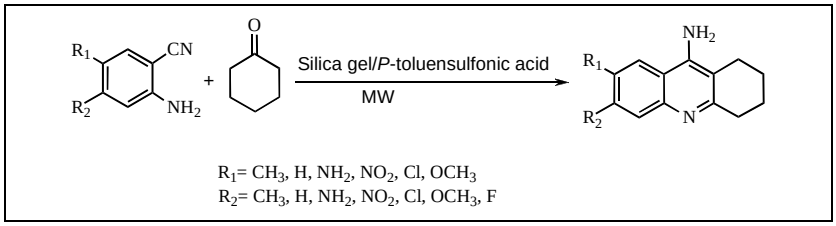

Effects of microwave irradiation on the solid-phase synthesis of tacrine and its derivatives have been evaluated. Preparation of tacrine analogues under conventional conditions suffers from poor synthetic efficiency and usually gives low yield. Reaction of substituted anthranilonitrile with cyclohexanone under microwave irradiation gave a good to excellent yield of the corresponding substituted 9-amino-1,2,3,4-tetrahydroacridines.

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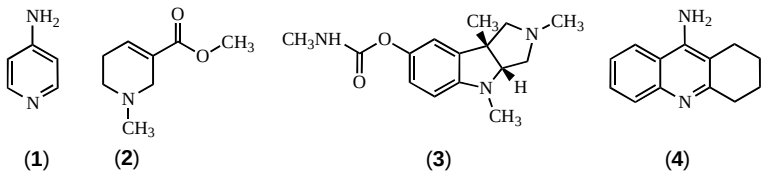
INTRODUCTION

Dementia is the most common psychiatric disorder of old age, and Alzheimer's disease [1] is its most common cause. Alzheimer's disease involves the degeneration of cholinergic neurones in the cerebral cortex and hippocampus, areas of the brain particularly associated with memory, higher intellectual functioning, and consciousness [2]. The biochemical deficits also extend into other neurochemical systems, affecting the levels of monoamine transmitters for example [3], but the most profound and consistent loss is that of cholinergic transmission. Consequently, much research concerns enhancing the cholinergic system in some way [4], ranging from the use of acetylcholine-releasing agents such as 4-aminopyridine (**1**) [5]; the acetylcholine precursor, choline [6]; cholinergic agonists, *e.g.* arecoline (**2**); and anticholinesterase drugs, *e.g.* physostigmine (**3**). However, one drug in particular has become the subject of intense pharmacological scrutiny for its efficacy in alleviating the symptoms of Alzheimer's disease, namely 9-amino-1,2,3,4-tetrahydroacridine, commonly referred to as tacrine (**4**) [7].

Tacrine (**4**) [8] was found to be a potent acetyl-cholinesterase inhibitor [9,10] in 1953 and, subsequently, an even stronger inhibitor of the butyrylcholinesterase family of enzymes [11]. More recently, tacrine has been shown to possess a much broader pharmacological profile than cholinesterase inhibition: blockage of potassium channels [12], inhibition of the neuronal monoamine uptake processes [13], and inhibition of monamine oxidase [14] have all been reported.

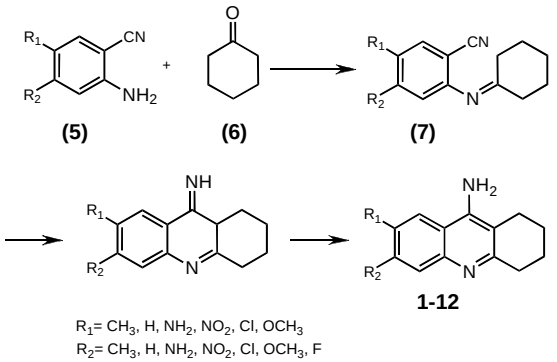
The study of tacrine analogues is still of interest to medicinal chemists involved in AD research. In this regard, we have studied the synthesis of tacrine derivatives under very mild and efficient conditions.



(**1**) (**2**) (**3**) (**4**)

Scheme1

Synthesis of tacrine analogues was generally reported by condensing of substituted anthranilonitrile (**5**) with cyclohexanone (**6**) in the presence of a Lewis acid. $ZnCl_2$ [15a], *P*-toluensolfunic acid (PTSA) [15b, 15c], BF_3/Et_2O [15d], and P_2O_5 [15e] were used as Lewis acid. Tacrine analogues were also prepared by condensing 2-amino-3-cyano-4*H*-pyrans with cyclohexanone [15f]. Amongst above procedures, the use of *P*-toluensolfunic acid is preferred because of its lower toxicity than other acids. However, all these methods suffer from low yield and long reaction time. The use of microwave irradiation to simplify and improve classical organic reactions has become a very popular technique because it often results in shorter reaction times, higher yields and cleaner reaction [16].



Scheme 2

On the other hand solvent-free chemical synthesis has received much attention recently [17]. Solvent-free processes are not only environmentally benign but also economical [18]. Since solvent is not required, toxic wastes can be minimized or eliminated and so the cost of solvent and waste treatment is reduced. Furthermore, operational simplicity is an attractive feature. Recent advances in this area include, for example, Aldol [19a,b] and related reactions [19c], asymmetric-catalyzed addition [19d] and catalyzed cross-coupling reactions [19e-h]. We now report here a simple and efficient method for preparation of tacrineanalogues *via* treatment of substituted anthranilonitrile (**5**) with cyclohexanone (**6**) using PTSA supported on silica gel under microwave irradiation (Scheme 2).

RESULTS AND DISCUSSION

The reaction of substituted anthranilonitrile (**5**) with cyclohexanone (**6**) was performed in a domestic microwave oven in sealed heavy-walled Teflon tubes (Scheme 2). When compounds (**5**), cyclohexanone and PTSA without silica gel were subjected to microwave irradiation, very low yield of corresponding tacrine was obtained. This result implies that silica gel plays an important role in this reaction. This was further confirmed when other solid supports such as montmorillonite K10, alumina and zeolite were employed. The results are shown in Table 1.

In order to find optimum condition for this synthesis we have treated 2-aminobenzonitrile (anthranilonitrile) with cyclohexanone using PTSA under microwave irradiation as a model experiment. As indicated in Table 1, when the reaction was conducted on acidic alumina or zeolite HY a moderate yield of tacrine was obtained after 12 minutes irradiation at 440 or 600W (Table 1, entries 1-4). When montmorillonite K10 clay was employed only low yield of tacrine was formed (Table 1, entries 5,6).

A quantitative yield of tacrine was gained when silica gel used as a solid support in this reaction (Table 1, entries 7, 8). No evidence of by-product formation was found in any case.

It is noteworthy from a mechanistic view point that an intermediate probably 2-cyclohexylideneamino-benzonitrile (**7**) [10d] was first formed which then converted to tacrine. To continue our systematic study of the cyclization reaction and to further appraise the influence of the silica gel on the outcome of the reaction, we have modified the relative ratios of reagents and catalyst. While maintaining a 1.5 molar excess of PTSA (0.26 g, 1.5 mmol) to anthranilonitrile (1 mmol) and cyclohexanone (1.2 mmol), the amount of silica gel was varied between 0.1 and 0.6 g. The results are clear-cut: the rate of tacrine formation steadily increases with the quantity of silica gel used. A 2:1 silica gel:PTSA weight ratio was required in order to achieve a quantitative conversion of anthranilonitrile within a few minutes.

In order to investigate the generality and applicability of this procedure we have carried out the reaction of substituted anthranilonitrile with cyclohexanone under optimum conditions. As a comparison, the PTSA mediated cyclodehydration reaction between anthranilonitrile with cyclohexanone which gave tacrine (**4**) [15b] was adopted to produce the ranges of compounds by substituting anthranilonitrile (**5**) (Scheme 2). The results are presented in the Table 2.

As indicated in this Table reaction of substituted anthranilonitrile with cyclohexanone using PTSA under conventional conditions usually gives low yield of corresponding tacrine derivatives in long reaction time (Table 2, entries 1-12). On the other hand these reactions

Table 1
Comparison of various solid supports for tacrine synthesis

Solid support	Entry	Power (W)	yield[a] %		
			4min	8min	12min
Alumina (acidic)	1	440	15	65	70
	2	600	20	70	70
Zeolite HY	3	440	20	75	75
	4	600	20	75	75
Montmorillonite (K-10)	5	440	30	70	85
	6	600	Trace	80	85
Silica gel	7	440	Trace	40	95
	8	600	50	95	>95

a) Isolated yield.

under microwave irradiation using PTSA supported on silica gel gives moderate to high yield of products in a much shorter reaction time (Table 2, entries 1-12).

In conclusion, we have described a rapid, novel and efficient method for condensation of substituted anthranilonitrile and using the solid catalyst PTSA/silica gel under microwave irradiation which forms tacrine analogues exclusively in moderate to high yield and high purity. Also, the unfavourable use of the aromatic solvents such as xylene was avoided. Several advantages like inexpensive and nontoxic catalyst; very short reaction time, cleaner conversion, one step process and operational simplicity make our method a useful procedure for this synthesis.

Table 2
Synthesis of tacrine analogues under conventional heating and microwave irradiation

Entry	R_1	R_2	Isolated yield%[a] Thermal heating	Isolated yield%[a] Microwave	m.p. °C[b]	Ref.
1	CH_3	H	35	65	223-225	20
2	H	CH_3	35	60	220-222	21
3	Cl	H	50	70	254-256	22
4	H	Cl	45	78	296-298	22
5	NO_2	H	40	65	264-266	23
6	H	NO_2	30	70	260-262	21
7	H	OCH_3	55	68	181-183	24
8	NH_2	H	60	75	118-120	25
9	H	F	40	65	210-212	25
10	Cl	Cl	40	65	265-267	21
11	OCH_3	OCH_3	45	80	275-277	24
12	H	H	70	95	120-122	15b

a) Yields refer to isolated products. b) All the products are known compounds were characterized by IR, ^{1}HNMR spectra and comparison with authentic samples.

EXPRIMENTAL

Solid supports: SiO_2 (mesh, 27-30), acidic alumina, and montmorillonite K10 were purchased from Fluka. Zeolite HY was received from Iranian National Oil Company. All the reactions were carried out in a domestic microwave oven: NN-C988 W model (2450 MHZ) in closed Teflon container (440-600W). Infrared (IR) spectra were recorded on Bruker VECTOR 22 spectrometer. ^{1}H NMR spectra were measured on a Bruker DRX500 AVANCE spectrometer, using $CDCl_3$ as solvent.

General Procedure for Preparation of Tacrine Derivatives. A: Under conventional conditions [15b,15c]. To a 25 ml, round-bottom flask equipped with Dean-Stark trap was charged PTSA (0.52 g, 3 mmoles), substituted anthranilonitrile (2 mmoles), cyclohexanone (0.24 g, 2.4 mmoles). The stirred solution was heated to reflux. At reflux, the water formed is removed by azeotropic distillation. The mixture was refluxed for another 10-15 hours (progress of reaction was monitored by TLC or GC). After cooling to room temperature, the crude product was isolated by filtration. Methanol (10 ml) was added to the filtrate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford pure products. Further purification can be carried out by extraction with dichloromethane and then by activated charcoal.

B: Under microwave irradiation. PTSA (0.26 g, 1.5 mmoles), substituted anthranilonitrile (1 mmoles), cyclohexanone (0.12 g, 1.2 mmoles) and solid supports (0.5-0.55 g) were thoroughly mixed in a mortar and exposed to microwave irradiation (600 W) in 2 minute intervals. After completion of the reaction (TLC), methanol (10 ml) was added and the mixture filtered. The resulting solution was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford pure products. All the products were characterized by their m.p, IR and ^{1}H NMR spectra and comparison with authentic samples.

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