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Synthesis of 2-(4-amino substituted benzylidene) indanone analogues from aromatic nucleophilic substitution (S_NAr) reaction

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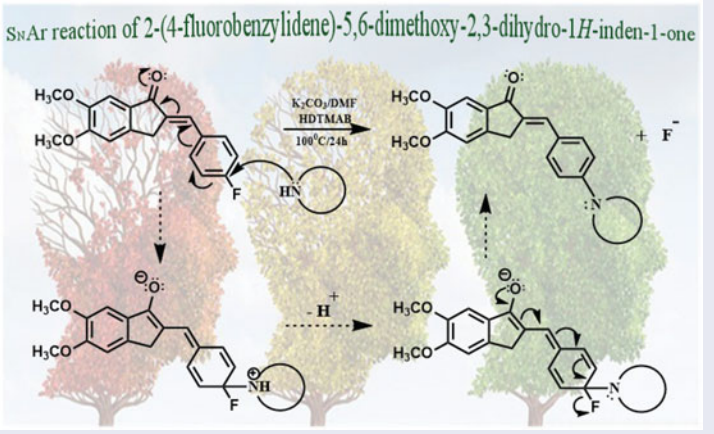
ABSTRACT

A novel, efficient and convenient procedure has been developed for the synthesis of 2-(4-amino-substituted benzylidene)indanone derivatives. In the first step, the reaction of 4-fluorobenzaldehyde with 5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one in the presence of NaOH in EtOH was described. In the next step, a variety of aliphatic and aromatic amines were reacted with 2-(4-fluorobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-Inden-1-one *via* aromatic substitution (S_NAr) reaction to produce 2-(4-aminobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-Inden-1-one derivatives as a novel class of 1-indanones. These products have been successfully prepared in good to excellent yields. ^{1}H and ^{13}C NMR, FT-IR spectroscopy and CHN analysis supported the proposed structures of the products.

GRAPHICAL ABSTRACT



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Introduction

1-Indanones are the important synthetic intermediates for agrochemical and pharmaceutical compounds as well as for olefin polymerization.[1] The indanone nucleus as a biologically active group is present in the structure of many drugs and biomaterials.[2] Synthetic indanone-based derivatives are known to have various pharmacological activities such as: diuretic, hypoglycemic, antihypertensive, antiproliferative, antimicrobial, acetylcholinesterase inhibitors, and in the treatment of Alzheimer's disease (AD) like donepezil hydrochloride (Aricept); for example, has a 1-indanone core.[3]

It is known that acetylcholinesterase (AChE) inhibitors are the first and the most developed group of drugs approved for AD treatment; tacrine, donepezil, and rivastigmine are well-known inhibitors.[4] Donepezil exhibits excellent effects in the early-to-moderate stages of AD patients. The benzylpiperidine and 5,6-dimethoxyindanone moieties of donepezil interact with the peripheral and central binding site of AChE separately.[5,6] There are various routes to synthesize donepezil in the literature, but these procedures have certain disadvantages, such as expensive catalysts, multiple reduction steps, side products, and low yields.[7,8] Due to these disadvantages, development of novel, simple, and efficient routes for the synthesis of donepezil and donepezil-like analogs continues to attract a great deal of interest for scientists.[9–11]

These observations encouraged us to design and synthesize new donepezil analogs via a S_NAr reaction (Fig. 1), in which the 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one ring was retained as the main core and new side-chains with various amine groups were substituted at the *para* position of the benzylidene group. In our previous report,[12] we demonstrated that this class of compounds could be prepared using an *N*-arylation reaction catalyzed by CuI. In this work, we decided to examine the S_NAr reaction for the synthesis of these types of donepezil analogs.

Results and discussion

Aryl-nitrogen bonds are prevalent in many compounds with pharmaceutical and biological interest. The development of synthetic methods to form these bonds has been widely studied. The aromatic nucleophilic substitution has been a powerful method for introducing an amine group in place of a halogen atom in some aryl halides, particularly fluorides. Therefore, as a starting point, we synthesized 2-(4-halobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one according to the procedure optimized in reference[12] as our main starting materials (Scheme 1). We know that the S_NAr reaction is a

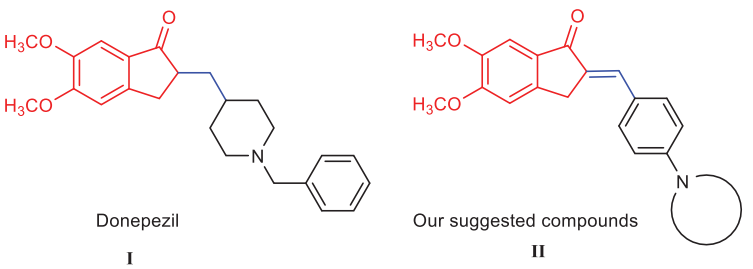
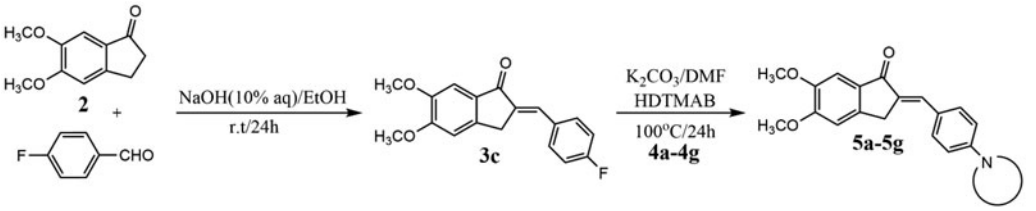
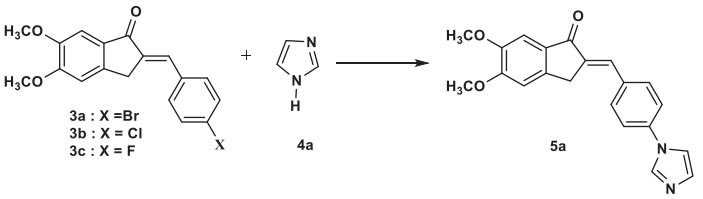


Figure 1. Structure of donepezil (I) and our suggested compounds (II).



Scheme 1. Synthesis of 2-(4-aminobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one.

Table 1. Various used conditions in the S_NAr reaction.



Entry	X	Solvent	Base	Catalyst	Temp (°C)	Yield (%)
1	F	Toluene	Cs_2CO_3	–	80	16
2	F	DMSO	Cs_2CO_3	–	80	47
3	F	DMF	Cs_2CO_3	–	80	58
4	F	DMF	Na_2CO_3	–	80	48
5	F	DMF	K_2CO_3	–	80	65
6	F	DMF	K_2CO_3	–	100	68
7	F	DMF	K_3PO_4	–	80	60
8	F	DMF	KOH	–	80	18
9	F	DMF	K_2CO_3	HDTMAB	80	75
10	F	DMF	K_2CO_3	HDTMAB	90	81
11	F	DMF	K_2CO_3	HDTMAB	100	87
12	Cl	DMF	K_2CO_3	HDTMAB	100	53
13	Br	DMF	K_2CO_3	HDTMAB	100	23

transition metal-free carbon-heteroatom bond formation. In general, the S_NAr reaction requires harsh conditions, a suitable base to enhance the nucleophilicity and an activating group such as a nitro and cyano substituent on the aryl halide to stabilize the S_NAr Meisenheimer complex.[13] In our compounds, the conjugation of the double bond with the carbonyl group withdraws electron density in the aromatic ring. C2 and C4 are highly electrophilic sites. Thus, a C4 halide can be displaced by a nucleophile in an addition-elimination S_NAr process.

As a model compound, we optimized the S_NAr reaction feasibility of the 2-(4-halobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one (**3a-c**) with imidazole (**4a**) as shown in Table 1. The aromatic nucleophilic substitution was studied using a variety of solvents, bases, and ligands at different temperatures. The results show that among various solvents and bases screened at 80 °C, the best result was obtained when DMF and K_2CO_3 were used as a solvent and the base, respectively (Table 1, entry 5). It was also observed that hexadecyltrimethylammonium bromide (HDTMAB) facilitated the S_NAr reaction of **3a** and (to some extent) **3 b**,[12] allowing *N*-arylation without added CuI in good yield (Table 1, entry 9).

The reaction was studied at different temperatures and 100 °C was selected as the optimal temperature (Table 1, entry 11). Thus, a catalyst system consisting of

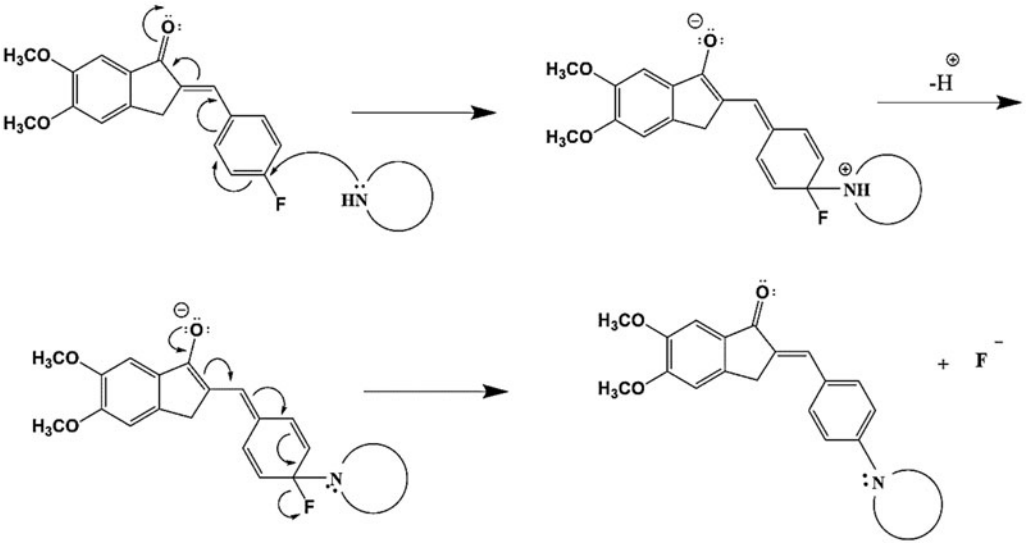


Figure 2. Addition- elimination mechanism of S_NAr reaction with 2-(4-fluorobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one.

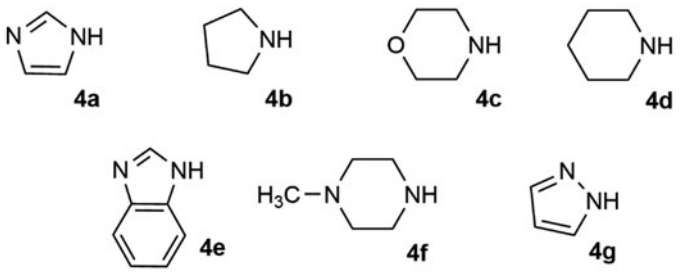


Figure 3. Aliphatic and aromatic used amines.

HDTMAB, and K_2CO_3 in DMF at 100 °C was employed for further studies. As expected, comparing the results of using different halobenzaldehydes (Table 1, entries 11–13), shows that yield of fluoro derivative (**3c**) is much higher than that of the corresponding bromo and chloro analogs for the S_NAr reaction. While fluoride is the worst leaving group for the SN_2 reaction, it is the best for the S_NAr reaction due to its small size (does not impede approach of the nucleophile) and electronegativity (imparts partial positive charge) to the carbon. Based on these facts, the fluorine atom could accelerate the first step in the addition-elimination mechanism (Figure 2).

To explore the scope and generality of this optimized condition, we extended this method to the synthesis of the corresponding indanone derivatives (**5**) via the S_NAr reaction between the 2-(4-fluorobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1*H*-inden-1-one and a variety of aliphatic and aromatic amines (Fig. 3).

As shown in Figure 4, the reactions were carried out efficiently and the desired products were produced in good yields (79–87%). The availability of 4-fluorobenzaldehyde as a starting material, the use of inexpensive reagents, and higher total yields of final products are some advantages of this method over previous reports.

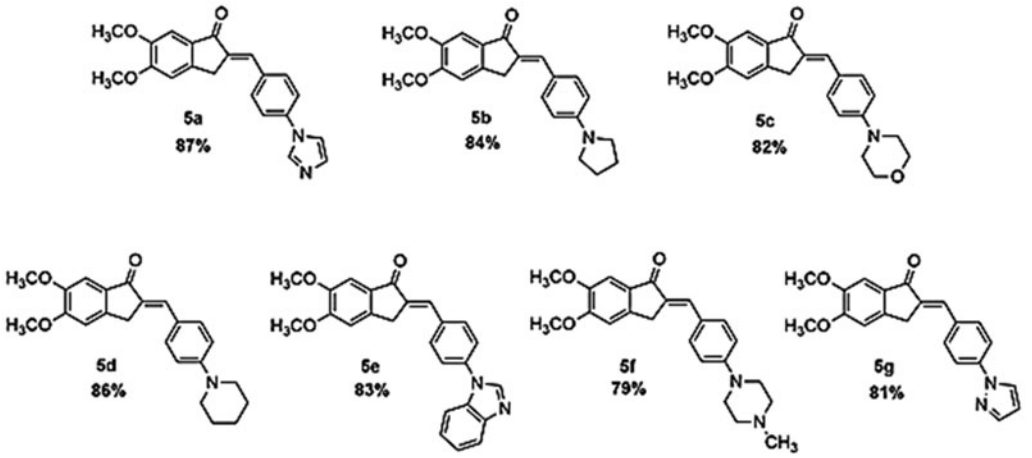


Figure 4. Final synthesized compounds (5a–5g).

Experimental

Solvents and reagents were purchased from Merck, Fluka, Sigma, Aldrich, and Yantai Suny Chem. International Co., Ltd. Commercially solid reagents were used without further purification. Column chromatography was performed on silica gel 60 (Merck, grain size 63–200 μm). All reactions were carried out under an atmosphere of argon. The ^{1}H NMR spectra were recorded using a Bruker FT-400 MHz spectrometer at room temperature, ^{13}C NMR spectra were determined on the same instrument at 100 MHz and with $CDCl_3$ as a solvent while chemical shifts are presented in delta values expressed in ppm referenced to $CHCl_3$ residue at 7.25 and 78 ppm. The FT-IR spectra were recorded on a Bruker–Tensor 270 spectrophotometer as KBr disks or as thin films between salt plates. Melting points were determined on a MEL-TEMP model 1202 D apparatus and are uncorrected.

General procedure for the synthesis of compound (3)

To a stirred solution of 4-halobenzaldehyde (1 mmol) and indanone (1 mmol) in EtOH (10 mL), an aqueous solution of NaOH (10%) was added dropwise. The reaction mixture was stirred overnight at room temperature. The obtained solid was collected by filtration and purified by recrystallization from EtOH to give desired product as a pure solid.

2-(4-Fluorobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1H-inden-1-one (3c)

Pale yellow solid; Yield 85%; mp: 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63–7.65 (2 H, d, $J = 8.6$ Hz, Ar–H), 7.61(1 H, s, methine–H), 7.13–7.15 (2 H, d, $J = 8.6$ Hz, Ar–H), 7.11(1 H, s, Ar–H), 6.97 (1 H, s, Ar–H), 3.99 (3 H, s, O–CH_3), 3.94 (3 H, s, O–CH_3), 3.93 (2 H, s, –inden–CH_2); FT-IR (KBr): 2958, 1691, 1591, 1490, 1302, 1224, 1085 cm^{-1}.

General procedure for the synthesis of compounds (5)

To a solution of **3c** (2 mmol), amine (4 mmol) in DMF (3 mL), K_2CO_3 (4 mmol), and HDTMAB (0.001 mmol) were added and the reaction mixture was heated at 100 °C for 24 h. When the reaction was complete (by TLC), the reaction mixture was cooled, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane, 2:8) to give the desired products.

2-(4-Imidazolobenzylidene)-5, 6-dimethoxy-2, 3-dihydro-1H-inden-1-one (5a)[12]

Yellow solid; Yield 87%; mp: 223–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91(1 H, s, methine–H), 7.71–7.73 (2 H, d, $J = 8.2$ Hz, Ar–H), 7.55 (1 H, s, Ar–H), 7.44–7.46 (2 H, d, $J = 8.2$ Hz, Ar–H), 7.32 (1 H, s, Ar–H), 7.31(1 H, s, Ar–H), 7.22 (1 H, s, Ar–H), 6.96 (1 H, s, Ar–H), 3.98 (3 H, s, O–CH_3), 3.93 (3 H, s, O–CH_3), 3.92 (2 H, s, indene–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 191.7, 154.5, 148.7, 143.6, 136.4, 135.1, 134.3, 133.7, 130.8, 129.9, 129.8, 129.5, 126.0, 120.3, 116.7, 106.1, 104.0, 55.2, 55.1, 31.0; Anal. Calcd. For $C_{21}H_{18}N_2O_3$: C, 72.89; H, 5.25; N, 8.09; Found: C, 72.61; H, 5.27; N, 8.06%; FT-IR (KBr): 2935, 2838, 1688, 1635, 1497, 1303, 1250, 1093 cm^{-1}.

Conclusion

In this study, an efficient and convenient method was described for the synthesis of 2-(4-aminobenzylidene)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-ones as drug scaffolds (**5a–g**), starting from 4-fluorobenzaldehyde and 5,6-dimethoxy-2,3-dihydro-1*H*-indene-1-one (**2**). Nucleophilic aromatic substitution of compound **3c** with a variety of aliphatic and aromatic amines resulted in the corresponding final products. ^{1}H NMR, ^{13}C NMR, FT-IR and CHN supported the assigned structures of the products. This method provides a convenient synthetic route to a variety of substituted indanone derivatives in good yields.

Supporting information

Supplementary data (general experimental details, characterization data) copies of the FT-IR, ^{1}H NMR, ^{13}C NMR and CHN analysis of all the synthesized donepezil analogues associated with this article can be found, in the online version.

Funding

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