Convenient Preparation of 1-Amidoindenes

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Lewis acid-catalyzed α-amidoalkylation of enolizable aldehydes with *N*-(α-benzotriazolyl-α-arylalkyl)amides followed by intramolecular Friedel−Crafts cyclization provides a convenient route to 2-substituted 1-amidoindenes.

Introduction

Although indene chemistry has a very long history, functionalized indenes and indanes have only recently begun to receive detailed attention from both medicinal and industrial chemists. 1-Aminoindanes are effective dopamine re-uptake blockers,[1] active against neurological disorders and neurotrauma[2] and, as their sulfonylated derivatives, are potential potassium channel blockers.[3] Cyano- and chloro-polysubstituted indenes can form self-organized supramolecular assemblies and thus be used as constituents for discotic liquid crystals.[4] 3-(ω-Phthalimidoalkyl)indenes undergo intramolecular cyclization upon irradiation and are useful intermediates in the synthesis of biologically active polycyclic compounds.[5]

Classically, indenes are prepared by intramolecular Friedel−Crafts alkylation of an appropriately located aromatic ring with vinylic or allylic carbocations generated in situ by (i) acid-catalyzed treatment of aryl-substituted allyl alcohols,[6] (ii) pyrolysis of the corresponding magnesium alkoxides,[7] (iii) cyclization of chalcones[8] or β-aralkyl carbonyl compounds,[9] (iv) ring-opening of 5-arylfuranones,[10] or (v) from 3,5,5-triaryloxazolidines.[11] Further approaches include (vi) Lewis acid-catalyzed reactions of substituted benzyl chlorides with alkynes,[12] (vii) condensation of alkynes with aryl ketones intramolecularly under irradiation[13] or intermolecularly in the presence of a (tetracarbonyl)manganese catalyst[14] to afford the corresponding 1-hydroxyindenes, and (viii) ring contraction of arynes under flash-vacuum pyrolysis to form unstable 1-vinylideneindenes.[15]

3-Aminoindenes, as enamines, are readily available from 2,3-dihydro-1*H*-inden-1-one and secondary amines,[16] and base-catalyzed cyclizations of aromatic α-ketonitriles give 3-aminoinden-1-ones.[17] Routes to 1- and 2-amino- or -amidoindenes are less obvious, although they are potential precursors for rhoeadine, isopavine, and cephalotaxime alkaloids.[18] Acid-catalyzed condensation of α-alkylcinnamaldehydes with carbamates gives hemiaminals, which cyclize to 2-alkyl-1-(alkoxycarbonylamino)indenes.[19] Regioselective ring opening−ring closure of 1-amino-2,3-diarylpropenes in a basic medium forms 1-amino- or 2-aminoindenes depending on the conditions.[20] 1-Aminoindene(tricarbonyl)chromium complexes are formed in thermal[21] or photochemical[22] reactions of alkynes with pentacarbonyl[amino(aryl)carbene]-chromiums. Previous acylation of the amino moiety in the organometallic reagent leads to 1-(alkoxycarbonylamino)indenes.[21]

Convenient access to 1-amino- and 1-amidoindenes could help to elucidate their properties (including biological activity) and potential utility. As enolizable β-aralkyl carbonyl compounds in the presence of a Lewis acid undergo intramolecular cyclization to indenes,[9] intramolecular Friedel−Crafts reaction of β-amido-β-aryl-aldehydes or -ketones **3** (R^3 = Ar) (Scheme 1) could result in 1-amidoindenes.

The good leaving ability of the benzotriazolyl moiety[23] enables its displacement in *N*-(α-benzotriazolylalkyl)-

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Scheme 1

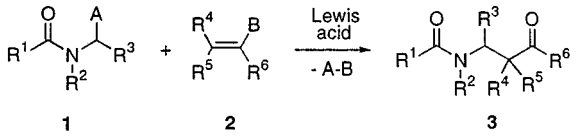

Table 1. Preparation of *N*-(α-Benzotriazolylalkyl)-Substituted Amides 6

compd	R	X	Y	yield, %	mp, °C (lit. mp, °C)
6a	Me	H	H	55	153−154 (154−156[28b])
6b	Me	Cl	H	65	146−147
6c[a]	Me	H	Cl	35	210 dec
6d	Me	Me	H	73	182−183 (186−189[28a])
6e	Me	MeO	H	62	186−187 (183−185[24b])
6f	Me	NO_2	H	69	179−181
6g	Me	Me_2N	H	64	170 dec
6h	Ph	H	H	85	181−182 (188−190[28a])

[a] This compound is poorly soluble in common solvents and was used in the next step without additional purification and full characterization.

substituted amides (**1**, A = Bt) in reactions with *C*-nucleophiles including (i) active methylene and methine compounds,[24] (ii) propen-2-yl acetate (one example),[25] and (iii) alkyl vinyl ethers, silyl enol ethers, and enamines under mild conditions ($ZnBr_2/CH_2Cl_2$, 40 °C) (**2**, B = OEt, $OSiMe_3$, NR_2).[26] Reactions of class (iii) provide convenient syntheses of β-amido aldehydes and β-amido ketones of type **3** which expand and complement previous amidoalkylation of derivatives **2** (A = OH, OMe, Cl) (for a review see[27]).

Thus, based on the literature data discussed above, we reasoned that the condensation of benzotriazole-containing amides with enolizable aldehydes in the presence of a Lewis acid should allow the development of a new synthetic route to β-amido aldehydes in accordance with Scheme 1 (A = Bt, B = OH). Subsequent cyclization under Friedel−Crafts conditions could provide a convenient approach to the preparation of various 1-amidoindenes.

Results and Discussion

Benzotriazolyl-substituted amides **6a**−**h** were prepared using the well-known Mannich three-component condensations of benzotriazole, amides **4a**,**b** and the appropriate aromatic aldehyde **5a**−**g** in the presence of catalytic *p*-toluenesulfonic acid (Table 1).[23] As found previously,[24b,28] the yields of amides **6a**−**h** are moderate to good (55−85%), except for the *o*-chloro derivative **6c**.

Amidoalkylations of enolizable aldehydes were studied using amide **6a** as a model. No reaction of **6a** occurred with hexanal under the conditions described for the reactions with methylene active compounds[24b] or silyl enol ethers,[26] in presence of zinc bromide at reflux in benzene or at reflux in 1,1,1-trichloroethane. In all these experiments, hexanal underwent aldol condensation while the amide **6a** was recovered intact. Refluxing a mixture of **6a** and hexanal in toluene in the presence of zinc bromide or boron trifluoride etherate for 5 h formed only trace amounts of product, the hexanal underwent aldol condensation and the amide was decomposed. However, providing a constant large excess of the *N*-(α-benzotriazolylalkyl)amide with respect to the aldehyde during the first stage of the reaction (by adding slowly a solution of hexanal in toluene−3 mmol−of the aldehyde in 20 mL of toluene during 1 h−to a refluxing mixture of the amide **6a** and zinc bromide−1 equiv−in toluene) led to the formation of product **7b** in 40% yield (Scheme 2). It seems that a β-amido aldehyde, formed as an intermediate under the reaction conditions, undergoes intramolecular Friedel−Crafts cyclization to give an indene derivative.

Scheme 2

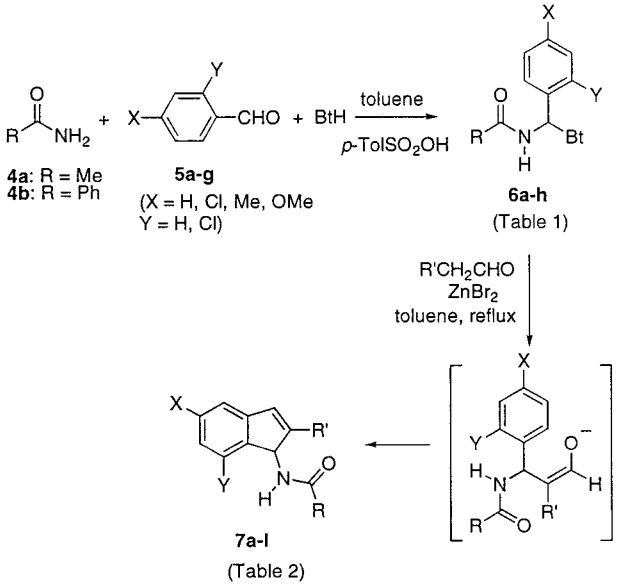

Table 2. Preparation of 1-Amidoindenes 7

run	compd	R	X	Y	R′	yield, %	mp, °C
1	**7a**	Me	H	H	Et	50	134−135
2	**7b**	Me	H	H	*n*-Bu	40	134−135
3	**7c**	Me	H	H	Ph	44	202−203
4	**7d**	Me	Cl	H	Et	51	176 dec
5	**7e**	Me	Cl	H	Ph	44	158−159
6	**7f**	Me	Cl	H	$PhCH_2$	39	158−159
7	**7g**	Me	H	Cl	Ph	38	220−221
8	**7h**	Me	Me	H	Et	27	163−164
9	**7i**	Me	Me	H	Ph	14	165 dec
10	**7j**	Me	Me	H	$PhCH_2$	33	143−145
11	**7k**	Ph	H	H	Ph	21	159 dec
12	**7l**	Ph	H	H	$PhCH_2$	24	121−122

The effect of the nature of a Lewis acid on the yield of the product was studied on the analogous reaction of **6a** with phenylacetaldehyde: zinc bromide in refluxing toluene provides the corresponding 1-amidoindene **7c** in 44% yield. Use of the less reactive Lewis acid, boron trifluoride etherate, decreased the yield to less than 10%. However, Lewis acids stronger than zinc bromide were also unsuccessful: thus, $SnCl_2$ or $TiCl_4$ led to fast decomposition of the starting amide **6a** under the reaction conditions and no product of type **7** was detected.

Amides **6b**,**c**, with mild electron-accepting substituents X or Y, afford indenes **7** in the same or higher yields as the analogous amides with X = Y = H (compare runs 1 and 4, or 3 and 5; Table 2). However, the introduction of electron-donating groups into the para position of the aromatic ring (X in **6d**,**e**) leads to a significant decrease in the product yield (compare runs 1 and 8, or 3 and 9; Table 2). The reaction with the anilino derivative (X = Me_2N) does not occur at all. As it is well-known that Friedel−Crafts alkylation is facilitated by electron-donating substituents, especially in the ortho and para positions of the aromatic ring, this led us to the conclusion that the rate-determining step in this reaction is the substitu-

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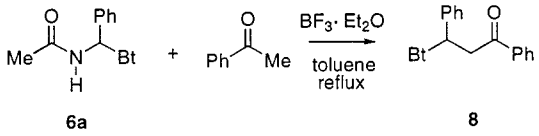
Scheme 3



tion of the benzotriazole moiety. It should also be noted that the increased reaction rate is crucial to obtain higher yields of the products because of the competing reactions of aldol condensation and starting amide decomposition.

However, contrary to our expectations, the reactions of **6** bearing a strong electron-accepting substituent ($X = NO_2$) failed to produce the corresponding 1-amidoindene, leading instead to the partial recovery of 4-nitrobenzaldehyde (in the reaction with volatile butyraldehyde) or its aldol condensation product (in the reaction with phenylacetaldehyde). These results could be explained by retro-Mannich reaction of the starting benzotriazolyl-substituted amide **6f** under the reaction conditions, and this conclusion was confirmed by a blank experiment of degradation of **6f** on heating in toluene in the presence of zinc bromide.

Replacement of the methyl group in the amide moiety by a phenyl group resulted in a significant decrease in the yield of the corresponding 1-amidoindenes (see Table 2).

When, instead of an aldehyde, a methyl ketone, such as acetophenone, was used in the reaction with **6a** under the conditions described above, only decomposition of the starting benzotriazolyl-substituted amide occurred. However, when, instead of zinc bromide, boron trifluoride etherate was applied as a Lewis acid, no benzotriazolyl group substitution was observed, but the product of the amido group substitution **8** was obtained in low yield (11%) (Scheme 3). Benzotriazole derivative **8** easily eliminates a molecule of benzotriazole during column chromatography on silica or alumina and even on storage at room temperature affording the corresponding chalcone. This has prevented the full characterization of **8**, which was identified only by means of ^{1}H and ^{13}C NMR spectroscopy after flash column chromatography. The aliphatic protons of the Bt-$CHCH_2$ fragment in the ^{1}H NMR spectrum display the characteristic ABX pattern with the following splitting constants: $J_{AB} = 18.0$ Hz, $J_{AX} = 8.8$ Hz and $J_{BX} = 4.9$ Hz.

In conclusion, we now report a tandem substitution-cyclization reaction of α-benzotriazolyl-substituted amides with enolizable aldehydes which provides a simple and convenient route to various 1-amidoindenes of type **7a**−**l**. Although the yields of amidoindenes **7** are moderate, this approach has some undoubtful advantages over the known methods for the preparation of analogous compounds (see, for example,[19,21]), such as the easy availability and high stability of the starting materials, the simplicity of the procedure and the mild reaction conditions.

Experimental Section

General Comments. Melting points were measured on a hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR data were recorded on 300 MHz NMR spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ as a solvent and with TMS as an internal standard. Column chromatography was carried out on silica gel (activated, neutral, 50−200 micron). Toluene was purified by distillation from Na under nitrogen. Benzotriazolyl-substituted amides **6** were prepared using the procedures already described.[28b]

General Procedure for the Synthesis of Substituted 1-Amidoindenes (7). A mixture of a benzotriazolyl-substituted amide **6** (2 mmol) and anhydrous zinc bromide (1 mmol) was heated in dry toluene (50 mL) until reflux. A solution of an aldehyde (3 mmol) in dry toluene (20 mL) was added dropwise to the refluxing reaction mixture during 1 h. The obtained reaction mixture was refluxed for another 4 h, then it was allowed to cool and washed successively with saturated aqueous NH_4Cl, water, saturated aqueous Na_2CO_3, and water. The organic extract was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography (silica, ethyl acetate/hexane = 1:1) and then recrystallized from ethanol to give the corresponding 1-amidoindene **7** as long white needles.

***N*-(2-Ethyl-inden-1-yl)acetamide (7a):** white needles; mp 134 °C (from EtOH); ^{1}H NMR δ 7.27 (d, $J = 7.0$ Hz, 1H), 7.20−7.02 (m, 3H), 6.35 (d, $J = 1.3$ Hz, 1H), 6.07 (d, $J = 9.1$ Hz, 1H), 5.49 (d, $J = 9.2$ Hz, 1H), 2.33−2.18 (m, 2H), 1.97 (s, 3H), 1.16 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR δ 170.8, 152.9, 144.1, 143.5, 127.8, 125.6, 124.5, 123.1, 120.1, 57.5, 23.0, 21.3, 12.3. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.51; H, 7.45; N, 6.95. Found: C, 77.08; H, 7.63; N, 7.04.

***N*-(2-Butyl-inden-1-yl)acetamide (7b):** white needles; mp 134−135 °C (from EtOH); ^{1}H NMR δ 7.36 (d, $J = 7.4$ Hz, 1H), 7.30−7.10 (m, 3H), 6.43 (s, 1H), 5.64 (d, $J = 9.5$ Hz, 1H), 5.35 (d, $J = 9.5$ Hz, 1H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.10 (s, 3H), 1.52−1.47 (m, 2H), 1.46−1.32 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR δ 170.5, 151.5, 144.2, 143.7, 128.1, 126.8, 124.8, 123.3, 120.3, 57.7, 30.4, 28.0, 23.4, 22.5, 13.9. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.37; N, 6.11. Found: C, 78.56; H, 8.91, N, 6.20.

***N*-(2-Benzyl-inden-1-yl)benzamide (7l):** white microcrystals; mp 121−122 °C (from EtOH); ^{1}H NMR δ 7.58 (m, 2H), 7.45−7.52 (m, 1H), 7.35−7.42 (m, 3H), 7.16−7.30 (m, 7H), 7.12 (dt, $J = 7.3$, 1.5 Hz, 1H), 6.44 (s, 1H), 5.89−5.98 (m, 2H), 3.79 (d, $J = 16.0$ Hz, 1H), 3.68 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR δ 167.8, 149.8, 144.3, 143.3, 138.9, 133.9, 131.6, 129.1, 128.9, 128.6(2), 128.5(2), 128.2, 126.9, 126.3, 125.3, 123.5, 120.7, 112.1, 58.4, 35.5. Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.90; N, 4.31. Found: C, 84.47; H, 5.96; N, 4.39.

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Supporting Information Available: Discussion of the characteristic features of NMR spectra of 1-amidoindenes and experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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