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Alan R. Katritzky [a] , Guifen Zhang [a] & Linghong Xie [a]
[a] Center for Heterocyclic Compounds, Department of Chemistry , University of Florida , Gainesville, FL, 32611-7200, USA
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NOVEL ROUTE TO FUNCTIONALIZED INDANS *VIA* FORMAL [3 + 2] CYCLOADDITIONS OF 1-BENZYLBENZOTRIAZOLES WITH ALKENES

Alan R. Katritzky*, Guifen Zhang and Linghong Xie

Center for Heterocyclic Compounds, Department of Chemistry,
University of Florida, Gainesville, FL 32611-7200, USA

ABSTRACT: α-Functionalized 1-benzylbenzotriazoles (**3**, **4** and **12**), derived from the lithiation of 1-(2,3-dimethoxybenzyl)benzotriazole **2** followed by reactions with electrophiles, or from the condensation of benzyl alcohol **11** with benzotriazole, undergo formal [3 + 2] cycloadditions with styrenes upon treatment with $ZnBr_2$ to give functionalized indans (**9**, **10**, **13** and **14**).

The indan ring system occurs in several natural products[1] and many indans show significant biological activity.[2] Accordingly, numerous methods for the construction of the indan skeleton have been developed.[3,4] Among these, approaches *via* formal [3 + 2] cycloaddition of benzyl cations with styrenes are perhaps the most general and straightforward.[3] The benzyl cations used in the aforementioned approaches are generated either from diphenylmethyl chlorides[3b,3c] or from quinone methides and benzyl alcohols.[3a] However, in both cases,

* To whom correspondence should be addressed

cycloaddition is successful only with styrenes possessing a β-substituent to slow down styrene polymerization. Moreover, the method using quinone methides and benzyl alcohols is restricted to the cases where a hydroxy group is located *para* to the benzyl cations.[3a]

In the course of our investigation on the use of benzotriazole derivatives in organic synthesis,[5] we found that the benzotriazolyl group is both a good anion-stabilizing group and a good leaving group. Due to these unique properties of the benzotriazolyl group, (benzotriazolylmethyl)indoles have been shown to be excellent precursors for the synthesis of 1-functionalized cyclopent[*b*]indoles *via* lithiation/alkylation and subsequent formal [3 + 2] cycloadditions with styrenes.[6] Our earlier work has also demonstrated that 1-benzylbenzotriazoles can be easily lithiated to give the α-carbanions, which upon reaction with α,β-unsaturated aldehydes and ketones, followed by acid-induced cyclization, lead to polysubstituted naphthalenes.[7] We now report that the anions derived from 1-benzylbenzotriazoles can react with electrophiles to give α-functionalized 1-benzylbenzotriazoles, which without separation undergo formal [3 + 2] cycloaddition with styrenes to provide 1-functionalized indans.

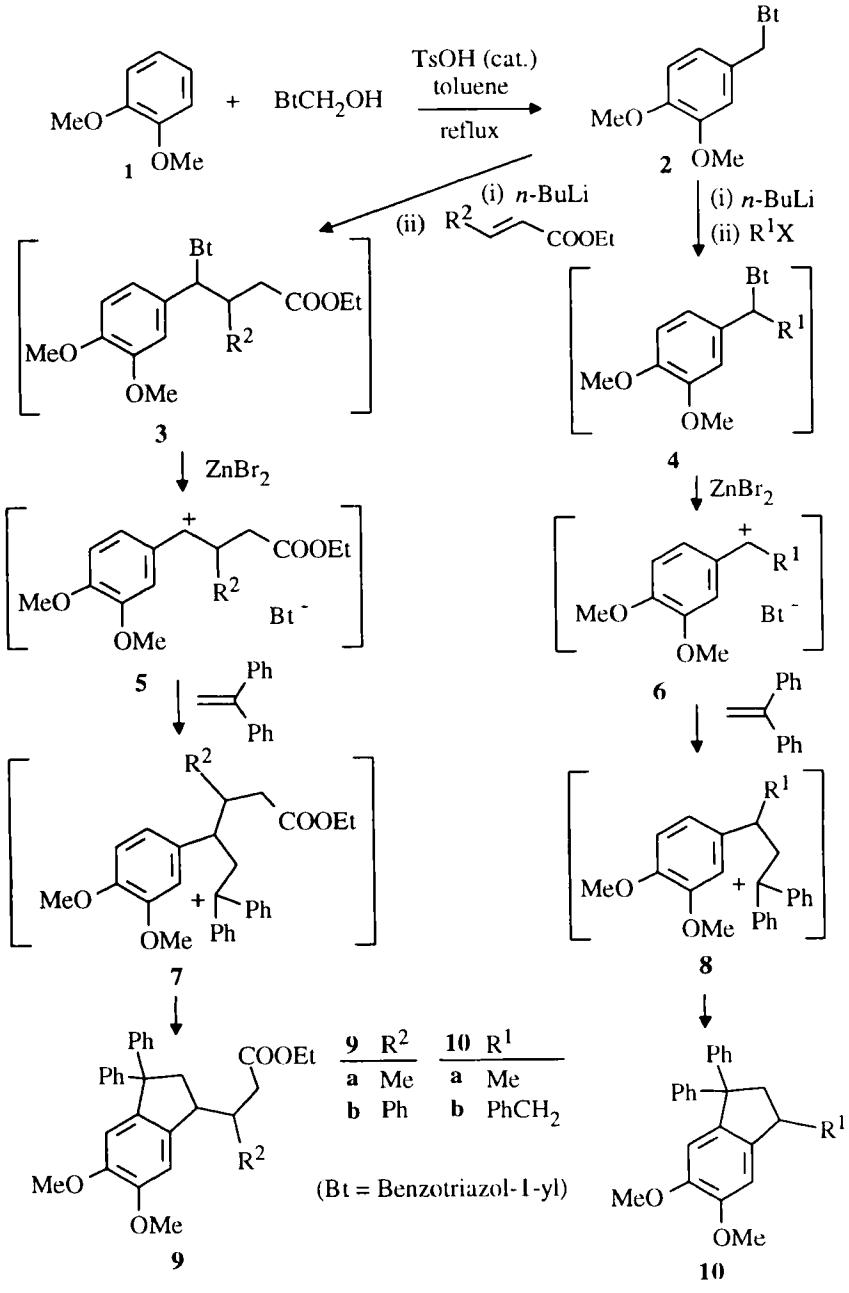
Results and Discussion

1-(3,4-Dimethoxybenzyl)benzotriazole (**2**) was prepared according to our previously reported procedure.[8] Treatment of **2** with *n*-butyllithium at -78 °C, under argon in THF, furnished a deep green solution of the corresponding α-carbanion, which reacted smoothly with alkyl halides (methyl iodide for **10a** and

benzyl bromide for **10b**) to give the alkylation products **4** (Scheme 1). After work-up, the crude compounds **4** were each treated with 1,1-diphenylethene and zinc bromide to furnish indans **10a** and **10b** in 61% and 78% overall yields from compound **2**. Similarly, when the anion of **2** was treated with α,β-unsaturated esters (ethyl crotonate for **9a** and ethyl cinnamate for **9b**), after cycloaddition with 1,1-diphenylethene in the presence of zinc bromide, functionalized indans **9a** and **9b** were obtained in 41% and 48% overall yields from **2**. Compounds **9a,b** and **10a,b** are all novel and were characterized by their ^{1}H and ^{13}C NMR and elemental analyses. Indans **9a,b** and **10a,b** are believed to arise from ionization of intermediates **3** and **4** to afford benzyl cations **5** and **6**, which then undergo successive trapping by a styrene to afford new benzyl cations **7** and **8**, and cyclization to the desired indans. In accordance with previous observations,[9] zinc bromide played a vital role in assisting the departure of the benzotriazolyl group.

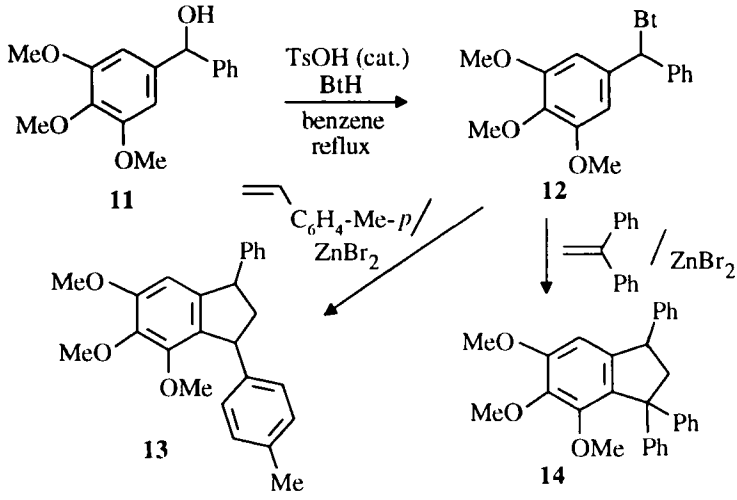
Mechanistically, ring closure of the benzylic cations (**7** and **8**) could occur either at the 2-positions (*ortho*-directing) or at the 6-positions (*para*-directing). However, in all cases, single regioisomers (**9a,b** and **10a,b**) were obtained. The other possible regioisomers from ring closure at C2 were not detected. The two 1H singlets (4,7-protons) in the region of 6.5-7.0 ppm in the ^{1}H NMR spectra of the products are characteristic of indans **9a,b** and **10a,b** from cyclization at C6.

To explore the versatility of this methodology, aldehydes and ketones were used as electrophiles. However, while the anion of **2** appeared to react with benzaldehyde and cyclohexanone to give the expected intermediates as judged from the NMR spectra of the crude products, attempted cycloadditions of the intermediates with 1,1-diphenylethene were unsuccessful, although in each case a trace of desired indan was detected by GCMS. The presence of a labile hydroxy group might be responsible for the failure.



Scheme 1

1-Benzylbenzotriazole **12** was prepared from the condensation of (3,4,5-trimethoxyphenyl)(phenyl)methanol with benzotriazole in the presence of a catalyst amount of *p*-toluenesulfonic acid in benzene (Scheme 2). Its structure was confirmed by its NMR and CHN analysis. Treatment of compound **12** with zinc bromide and the appropriate styrene (4-methylstyrene for **13** and 1,1-diphenylethene for **14**) afforded indans **13** and **14** in 74% and 94% yields, respectively. Compounds **13** and **14** are new and were characterized by NMR and CHN analysis or HRMS.



Scheme 2

As mentioned in the introduction, benzyl cations generated from benzyl alcohols[3a] and benzyl chlorides[3b,3c] can undergo successful [3 + 2] cycloadditions only with β-substituted styrenes. In contrast, 1-benzylbenzotriazoles can readily react with β-unsubstituted styrenes as demonstrated by the synthesis of indans **9a,b** and **10a,b**, and the successful cycloadditions of 1-[1-phenyl-1-(3,4,5-trimethoxyphenyl)methyl]benzotriazole (**12**) with 4-methylstyrene and 1,1-diphenylethene. Interestingly, while reactions of 1-benzylbenzotriazoles with β-

unsubstituted styrenes were successful, the use of β-substituted styrenes (*e.g.* β-methylstyrene) provided no detectable desired indan.

In conclusion, a facile route to functionalized indans has been developed *via* formal [3 + 2] cycloadditions of 1-benzylbenzotriazoles and styrenes. Compared with the analogous methods previously developed using diphenylmethyl chlorides[3b,3c] or quinone methides and benzylic alcohols,[3a] our approach complements them by taking advantage of the ready introduction of functionality into the 1-position of indans and the successful application to β-unsubstituted styrenes.

Experimental Section

Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen from sodium/benzophenone immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. 1-(3,4-Dimethoxybenzyl)benzotriazole (**2**) was prepared according to previously reported procedure.[8]

General Procedure for the Preparation of Indans **9a,b** and **10a,b**.

To a solution of 1-(3,4-dimethoxybenzyl)benzotriazole (**2**) (1.1 g, 4 mmol) in THF (75 mL) at -78 °C under argon was added *n*-BuLi (2 *M*, 2.2 mL, 4.4 mmol). After 1 h, a solution of an appropriate electrophile (ethyl crotonate for **9a**, ethyl cinnamate for **9b**, methyl iodide for **10a**, and benzyl bromide for **10b**) (4.4

mmol) in THF (2 mL) was added. The mixture was stirred at -78 °C for an additional 4 h. Water (60 mL) and diethyl ether (100 mL) were added to the mixture and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the combined organic layer was dried over $MgSO_4$. After the solvent was removed, the residue was dissolved in methylene chloride (50 mL). To the solution, 1,1-diphenylethylene (0.79 g, 4.4 mmol) and zinc bromide (1.8 g, 8 mmol) were added. The mixture was refluxed for 9 days. After the solid was filtered off, sodium hydroxide (aq. 1 *N*, 20 mL) was added to the filtrate. The organic phase was separated and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography (hexanes : ethyl acetate = 1 : 7) to give the pure product.

1,1-Diphenyl-3-[1-(ethoxycarbonyl)prop-2-yl]-5,6-dimethoxyindan (9a): obtained as a mixture (1:1) of two diastereoisomers, colorless oil (0.52 g, 41%); ^{1}H NMR δ 7.30-7.16 (m, 10H), 6.81 (s, 0.5H), 6.76 (s, 0.5H), 6.56 (s, 0.5H), 6.55 (s, 0.5H), 4.17-4.08 (m, 2H), 3.90 (s, 3H), 3.74 (s, 3H), 3.22-3.19 (m, 1H), 2.93-2.71 (m, 2H), 2.57-2.32 (m, 2.5H), 2.10-2.01 (m, 0.5H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 1.5 H), 0.90 (d, *J* = 6.6 Hz, 1.5H); ^{13}C NMR δ 173.5 [173.0], 148.8 [148.6], 148.3 [146.6], 141.4 [141.3], 136.5 [136.3], 128.3 [128.2], 128.1 [128.0], 127.9 [127.8], 126.0 [125.8], 109.3 [109.2], 106.6 [106.4], 60.2 [60.1], 56.0 (2C), 47.3 [46.0], 45.3 [44.2], 40.5, 36.7 [31.3], 31.2 [31.1], 18.8 [14.2], 14.1. HRMS calcd for $C_{29}H_{32}O_4$ 444.2301, found 444.2294.

1,1-Diphenyl-3-{[1-phenyl-2-(ethoxycarbonyl)]ethyl}-5,6-dimethoxyindan (9b): obtained as a colorless oil (0.63 g, 48%); ^{1}H NMR δ 7.31-7.06 (m, 12H), 7.00-6.95 (m, 4H), 6.40 (s, 1H), 3.96-3.87 (m, 2H), 3.93 (s, 3H), 3.70 (s, 3H), 3.48-3.42 (m, 1H), 3.37-3.30 (m, 1H), 2.95-2.69 (m, 3H), 2.54-2.47 (m, 1H), 1.03 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 172.1, 148.3, 147.5, 141.7, 136.4, 128.7, 128.6, 128.3, 128.0, 127.8, 126.4, 125.9, 125.8, 109.8, 108.1, 60.4, 60.1, 56.1, 56.0, 48.1, 47.7, 44.5, 39.4, 13.9. HRMS calcd for $C_{34}H_{34}O_4$ 506.2457, found 506.2460.

1,1-Diphenyl-3-methyl-5,6-dimethoxyindan (10a): obtained as a colorless solid (0.84 g, 61%); mp 109-110 °C; ^{1}H NMR δ 7.31-7.16 (m, 10H), 6.77 (s, 1H), 6.57 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.09-2.99 (m, 2H), 2.46-2.39 (m, 1H), 1.35 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 148.8, 148.5, 148.1, 146.7, 140.7, 140.1, 128.4, 128.3, 127.9, 127.8, 126.0, 125.9, 109.4, 106.3, 60.6, 56.2, 56.0, 53.2, 36.6, 19.0. Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.67; H, 7.14.

1,1-Diphenyl-3-benzyl-5,6-dimethoxyindan (10b): obtained as colorless plates (1.31 g, 78%); mp 122-123 °C; ^{1}H NMR δ 7.28-7.10 (m, 15H), 6.65 (s, 1H), 6.56 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.40-3.37 (m, 1H), 3.15 (dd, J = 13.6 and 6.3 Hz, 1H), 2.93 (dd, J = 12.8 and 6.5 Hz, 1H), 2.72 (dd, J = 13.6 and 9.1 Hz, 1H), 2.52 (dd, J = 12.8 and 8.7 Hz); ^{13}C NMR δ 148.4, 148.2, 146.8, 140.9, 140.4, 138.2, 128.9, 128.4, 128.2, 127.8, 127.8, 125.9, 109.3, 106.7, 60.4, 56.0, 55.7, 50.8, 43.7, 41.1. Anal. Calcd for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 86.13; H, 6.91.

Preparation of 1-[(3,4,5-trimethoxyphenyl)(phenyl)methyl]benzotriazole (**12**).

A solution of benzotriazole (5.2 g, 44 mmol), (3,4,5-trimethoxyphenyl)-(phenyl)methanol (11.0 g, 40 mmol) and *p*-toluenesulfonic acid (0.1 g) in benzene (150 mL) was refluxed for 3 days. After being cooled to room temperature, the solution was washed with aqueous sodium hydroxide (2 *N*, 2 × 100 mL) to remove excess benzotriazole. The benzene solution was extracted with cold hydrochloric acid (25%, 5 × 50 mL) to allow complete extraction of the product into the aqueous layer. To the combined aqueous extract was added water (500 mL), and the solution was extracted with benzene (3 × 100 mL). The combined benzene solution was washed with water (2 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave pure product (9 g, 60%); mp 134-135 °C; ^{1}H NMR δ 8.11-8.08 (m, 1H), 7.38-7.31 (m, 6H), 7.28-7.16 (m, 3H), 6.48 (s, 2H), 3.85 (s, 3H), 3.71 (s, 6H); ^{13}C NMR δ 153.4 (2C), 146.3, 137.6, 133.2, 133.0, 128.8, 128.5, 128.1, 127.4, 123.9, 120.2, 110.5, 105.7, 67.1, 60.8, 56.1. Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.25; H, 5.64; N, 11.13.

General Procedure for the Preparation of Indans **13** and **14**.

To a solution of 1-[(3,4,5-trimethoxyphenyl)(phenyl)methyl]benzotriazole (**12**) (0.75 g, 2 mmol) in methylene chloride (70 mL) at room temperature was added zinc bromide (0.9 g, 4 mmol) and an appropriate styrene (4-methylstyrene for **13** and 1,1-diphenylethene for **14**) (2 mmol). The mixture was refluxed for 3 days. After the solid was filtered off, sodium hydroxide (aq. 1 *N*, 20 mL) was added to the filtrate. The organic phase was separated and the aqueous layer was

extracted with diethyl ether (2 × 30 mL). The combined organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by column chromatography (hexanes : ethyl acetate = 7 : 1) to give the pure product.

1-Phenyl-3-(4-methylphenyl)-4,5,6-trimethoxyindan (13): obtained as a mixture (2:1) of two diastereoisomers, colorless oil (0.56 g, 74%); ^{1}H NMR δ (minor isomer in square bracket) 7.36-6.99 (m, 9H), 6.27 [6.31] (s, 1H), 4.38 [4.61] (t, J = 8.8 Hz, 1H), 4.27 [4.46] (t, J = 8.8 Hz, 1H), 3.80 [3.84] (s, 3H), 3.70 [3.72] (s, 3H), 3.35 [3.56] (s, 3H), 3.04-2.95 [2.55-2.50] (m, 1H), 2.10-1.99 [2.49-2.48] (m, 1H), 2.32 [2.31] (s, 3H); ^{13}C NMR δ 153.4 [153.7], 150.2 [149.7], 144.7 [144.9], 143.1, 142.7, 142.5, 135.4 [135.3], 131.4, 128.8 [128.9], 128.5 [128.4], 128.2 [128.1], 127.5 [127.1], 126.4 [126.4], 103.6, 60.7, 59.7 [60.2], 56.1, 51.3 [50.5], 48.5 [48.0], 47.2 [47.0], 21.0 [20.9]. HRMS calcd for $C_{25}H_{26}O_3$ 374.1882, found 374.1878.

1,1,3-Triphenyl-5,6,7-trimethoxyindan (14): obtained as a colorless solid (0.82 g, 94%); mp 189-190 °C; ^{1}H NMR δ 7.38-7.22 (m, 14H), 7.18-7.15 (m, 1H), 6.25 (s, 1H), 4.12 (dd, J = 10.0 and 6.0 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.28 (dd, J = 13.0 and 6.0 Hz, 1H), 3.10 (s, 3H), 2.93 (dd, J = 13.0 and 10.0 Hz, 1H); ^{13}C NMR δ 154.0, 150.4, 149.0, 144.6, 144.0, 142.1, 141.6, 134.4, 129.0, 128.6, 128.5, 127.9, 127.5, 126.6, 126.3, 125.6, 103.6, 60.8, 60.5, 59.2, 57.2, 56.0, 49.9. Anal. Calcd for $C_{30}H_{28}O_3$: C, 82.54; H, 6.46. Found: C, 82.39; H, 6.46.

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