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A novel alkyne-induced recyclization of 4-hydroxymethyl or 4-formyl-1*H*-2,3-dihydroisoindoles—an effective pathway to substituted isobenzofurans

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ABSTRACT

2-Alkyl or 2-benzyl-substituted 4-hydroxymethyl(formyl)isoindoles readily react with electron-deficient alkynes undergoing intramolecular cyclization to produce 1-aminomethyl-substituted isobenzofurans in good yields.

Recyclization reactions of carbo-, and especially heterocyclic compounds, are a valuable synthetic tool in organic chemistry. Recyclization in the presence of various nucleophiles, electrophiles, or dipolar reagents occurs via ring opening in the initial molecule followed by its subsequent closure. This process is often accompanied by ring expansion or contraction, introduction of a heteroatom in the ring or its replacement by another heteroatom, etc. Nevertheless, from a preparative viewpoint, all these complex transformations take place in a one-pot reaction, thus making possible effective syntheses of compounds that are difficult to obtain by other protocols.

Several transformations of this type are known, including the Hafner reaction,[1] the Dimroth,[2] Boulton–Katritzky,[3] Cornforth, and Kost–Sagitullin rearrangements.[4,5] Rearrangements of heterocyclic rings by temporary opening and subsequent closure to new molecules are of particular interest both synthetically and theoretically.

We have recently presented several examples of tetrahydropyrido-[6] and tetrahydroazepino-[7] annulated (hetero)cycle transformations promoted by activated alkynes to yield the N-containing ring expansion products. The present Letter reports on unusual recyclizations of related dihydroisoindoles **1**–**10** under the action of activated alkynes.

The starting 4-hydroxymethyldihydroisoindoles **1**–**8** required for the present study were obtained by $LiAlH_4$ reduction of the corresponding isoindole carboxylic acids, synthesized according to the procedure previously described[8] (Scheme 1, Table 1). Hydroxymethyl derivatives **3** and **6** were oxidized by pyridinium chlorochromate (PCC) to give the aldehydes **9** and **10** (see Supplementary data for details).

By analogy to the previously reported results[6,7,9] we expected that the reactions of **1**–**10** with activated alkynes would yield the corresponding benzazepine derivatives **A**, or, in the case of derivatives **9** and **10**, containing a potent electron-withdrawing group, the products of Stevens rearrangement of an intermediate ylide **B** (Scheme 2).

The reactions of dihydroisoindoles **1**–**7** with methyl propiolate (MP), dimethyl acetylenedicarboxylate (DMAD), or acetyl acetylene proceeded smoothly,[10] but to our surprise, none of the expected derivatives were obtained. The only products isolated in good preparative yields were substituted phthalan derivatives **11**–**17**, **19**, and **22**–**24**. (Scheme 3, Table 2). We presume that the reaction starts with the Michael addition of the alkyne to the tertiary N-atom of the starting compound followed by abstraction of H^+ from the hydroxy group in intermediate **C**. The resulting zwitterion **D** undergoes intramolecular recyclization to yield the phthalan derivatives **11**[11]–**17**, **19**, and **22**–**24** (Scheme 3).

In the case of *iso*-pentyl derivative **6**, a small amount of a debenzylation by-product, *N*-vinyl-substituted isoindole **18** was isolated. 2-Phenyl-substituted isoindole **8** was unreactive toward activated alkynes even under forcing conditions (48 h refluxing in methanol or acetonitrile, sixfold molar excess of alkyne). This is most likely due to the low basicity of the aniline nitrogen atom, which fails to undergo Michael addition with the alkyne. The proposed reaction mechanism is consistent with that reported for the synthesis of isobenzofuran derivatives by alkali-catalyzed transformations of dialkyl(4-hydroxy-2-butynyl)(3-alkenylpropargyl) ammonium salts.[12]

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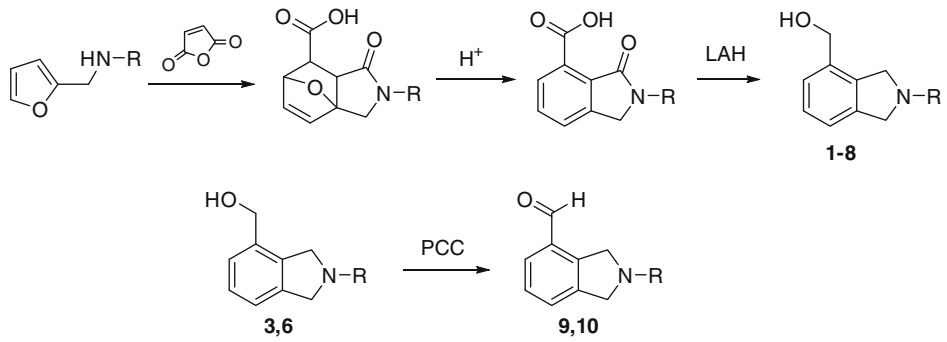
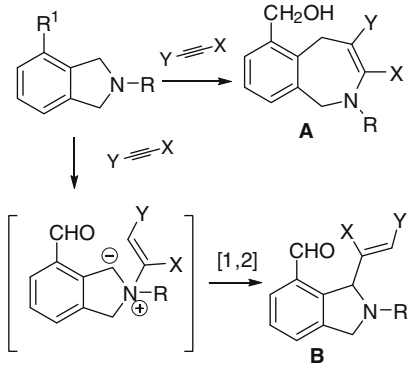


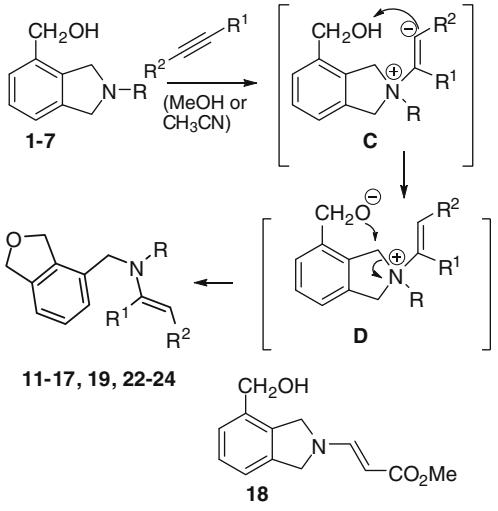
Scheme 1. Synthesis of the starting compounds.

Table 1
Characteristics of the starting compounds

Product #	R	Yield (%)	Mp (°C)
1	*i*-Pr	63	114–115
2	Bn	67	136–137
3	$(CH_2)_3OCH_3$	61	84–86
4	*i*-Bu	64	73–74
5	*i*-Pentyl	69	76–77
6	3,4-$(MeO)_2$ $C_6H_3CH_2$	71	140–141
7	$CH_2(CH_2)_3CH_3$	68	88–89
8	4-F-C_6H_4	73	127–128
9	$(CH_2)_3OCH_3$	30	Oil
10	3,4-$(MeO)_2C_6H_3CH_2$	32	Oil



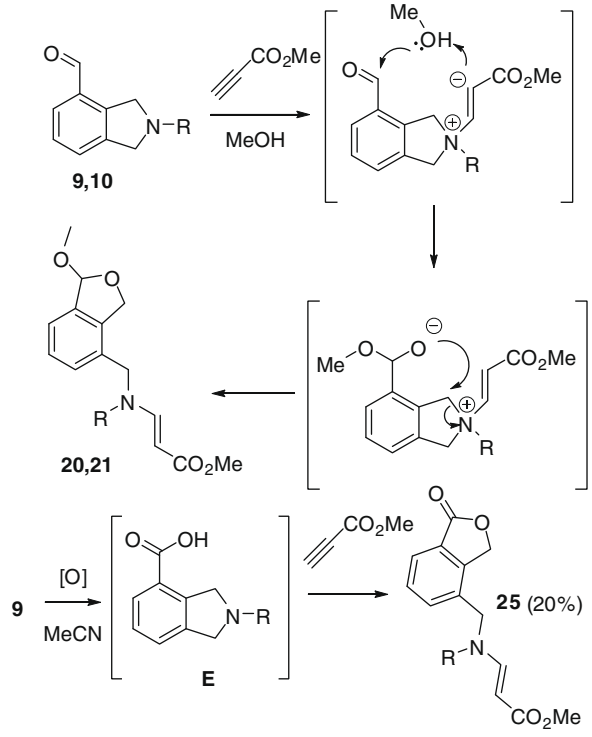
Scheme 2.



Scheme 3.

Table 2
Reactions of starting compounds **1**–**10** with alkynes

Product	R	R^1	R^2	R^3	Yield (%)	Mp (°C)
11	*i*-Pr	H	CO_2Me	H	64	99–101
12	*i*-Pr	CO_2Me	CO_2Me	H	67	175
13	*i*-Pr	H	COMe	H	50	Oil
14	*i*-Bu	H	CO_2Me	H	71	Oil
15	Bn	H	CO_2Me	H	64	133–135
16	$(CH_2)_3OCH_3$	H	CO_2Me	H	59	Oil
17	$(CH_2)_3OCH_3$	CO_2Me	CO_2Me	H	88	Oil
19	$CH_2(CH_2)_3CH_3$	H	CO_2Me	H	43	Oil
20	$(CH_2)_3OCH_3$	H	CO_2Me	OCH_3	36	Oil
21	3,4$(MeO)_2C_6H_3$	H	CO_2Me	OCH_3	40	Oil
22	*i*-Pentyl	H	CO_2Me	H	63	Oil
23	*i*-Pentyl	CO_2Me	CO_2Me	H	65	87–88
24	*i*-Pentyl	H	COMe	H	24	Oil
25	$(CH_2)_3OCH_3$	H	CO_2Me	=O	20	Oil



Scheme 4.

4-Formyl-substituted derivatives **9** and **10** reacted readily with MP in methanol at room temperature, providing cyclic semi-acetal derivatives **20**[13] and **21**, however, their reactions with MP in acetonitrile were not as efficient and required a rather long-reaction time (72 h). The only product that was successfully isolated from the reaction mixtures was the phthalide derivative **25**[14] (20%), which was most likely formed from the corresponding carboxylic acid **E**, generated in situ from **9** (Scheme 4).

In conclusion, we have reported a novel synthetic approach toward 4-aminomethyl-substituted dihydroisobenzofuran derivatives, based on a new alkyne-induced recyclization of easily available 4-hydroxymethyl(formyl) dihydroisoindoles. Work, aimed at exploring the reaction scope and limitations is underway and will be reported in due course.

Acknowledgment

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A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2009.06.036.

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10. General method for the reaction of **1**–**10** with activated alkynes. DMAD, methyl propiolate, or acetyl acetylene (2.5 mmol) was added to a solution of dihydroisoindole **1**–**10** (1.7 mmol) in methanol or acetonitrile (10 ml). The reaction mixture was stirred for 24–32 h at 25 °C (TLC monitoring). The solvent was evaporated under reduced pressure and the resulting residue was purified by flash column chromatography on SiO_2 with ethyl acetate as eluent to give isobenzofurans **11**–**25**.
11. *Methyl* (*E*)-*3-[1,3-dihydro-4-isobenzofuranylmethyl* (*isopropyl*)*amino]-2-propenoate* (***11***): white solid, mp 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 [d, 6H, *J* = 6.7 Hz, CH(CH_3)$_2$], 3.58–3.61 [m, 1H, *CH*(CH_3)$_2$], 3.63 (s, 3H, O*CH*$_3$), 4.16 (s, 2H, N*CH*$_2$), 4.53 (d, 1H, *J* = 13.1 Hz, =*CH*), 5.08 (s, 2H, *CH*$_2$O), 5.12 (s, 2H, *CH*$_2$O), 7.05 (d, 1H, *J* = 7.9 Hz, *CH*-Ar), 7.13 (d, 1H, *J* = 7.9 Hz, *CH*-Ar), 7.24 (t, 1H, *J* = 7.9 Hz, *CH*-Ar), 7.69 (d, 1H, *J* = 13.1 Hz, N–*CH*=) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 21.3 (2 × C), 31.1, 50.5 (2 × C), 54.7, 72.4, 73.8, 86.0, 120.1, 125.1, 128.3 (2 × C), 136.5, 150.2, 170.1 ppm. ESI MS 276 (M^++1). Anal. Calcd for $C_{16}H_{21}NO_3$ (275.34): C, 69.79; H, 7.69; N, 5.09. Found: C, 69.83; H, 7.64; N, 5.14.
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13. *Methyl* (*2E*)-*3-{[(1-methoxy-1,3-dihydro-2-benzofuran-4-yl*)*methyl](3-methoxypropyl*)*amino} acrylate* (***20***): yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.73–1.82 (m, 2H, *CH*$_2$-2), 3.20 (t, 2H, *J* = 5.6 Hz, *CH*$_2$-3), 3.30 (s, 3H, O*CH*$_3$), 3.33 (t, 2H, *J* = 5.5 Hz, *CH*$_2$-1), 3.45 (s, 3H, O*CH*$_3$), 3.66 (s, 3H, O*CH*$_3$), 4.27 (s, 2H, N*CH*$_2$), 4.65 (d, 1H, *J* = 13.1 Hz, *CH*=), 4.97 (d, 1H, *J* = 13.0 Hz, O*CH*), 5.11 (dd, 1H, *J* = 13.0 Hz, ^{4}*J* = 2.0 Hz, O*CH*,) 6.16 (d, 1H, ^{4}*J* = 2.0 Hz, *CH*OCH$_3$), 7.15–7.18 (m, 1H, *CH*-Ar), 7.33–7.34 (m, 2H, *CH*-Ar), 7.56 (d, 1H, *J* = 13.1 Hz, N–*CH*=) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 29.2, 50.2, 54.2 (2 × C), 54.7, 58.2, 68.8, 70.9, 84.9, 107.0, 122.0, 128.1, 132.8, 135.5, 136.8, 137.8, 151.5, 169.5 ppm. ESI MS 336 (M^++1). Anal. Calcd for $C_{18}H_{25}NO_5$ (335.17): C, 64.46; H, 7.51; N, 4.18. Found: C, 64.87; H, 7.13; N, 4.25.
14. *Methyl* (*2E*)-*3-{(3-methoxypropyl)[(1-oxo-1,3-dihydro-2-benzofuran-4-yl*)*methyl]-amino}acrylate* (***25***): yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.79–1.84 (m, 2H, *CH*$_2$-2), 3.23 (t, 2H, *J* = 6.6 Hz, *CH*$_2$-3), 3.31 (s, 3H, O*CH*$_3$), 3.37 (t, 2H, *J* = 6.6 Hz, *CH*$_2$-1), 3.67 (s, 3H, O*CH*$_3$)), 4.40 (s, 2H, *CH*$_2$N), 4.68 (d, 1H, *J* = 13.1 Hz, *CH*=), 5.25 (s, 2H, *CH*$_2$O), 7.50 (t, 1H, *J* = 7.9 Hz, *CH*-Ar), 7.61–7.56 (m, 2H, *CH*-Ar and N*CH*=), 7.87 (d, 1H, *J* = 7.9 Hz, *CH*-Ar) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 28.7, 50.8, 51.7, 53.3 (2 × C), 58.7, 68.7, 70.4, 86.1, 122.3, 123.9, 130.1, 133.1 (2 × C), 149.1, 169.5, 171.4. ESI MS 320 (M^++1). Anal. Calcd for $C_{17}H_{21}NO_5$ (319.14): C, 63.94; H, 6.63; N, 4.39. Found: C, 64.35; H, 6.25; N, 4.47.