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Silica Gel-Mediated Hydroamination/Semipinacol Rearrangement of 2-Alkylaminophenylprop-1-yn-3-ols: Synthesis of 2-Oxindoles from Alkynes and 1-(2-Aminophenyl) Ketones

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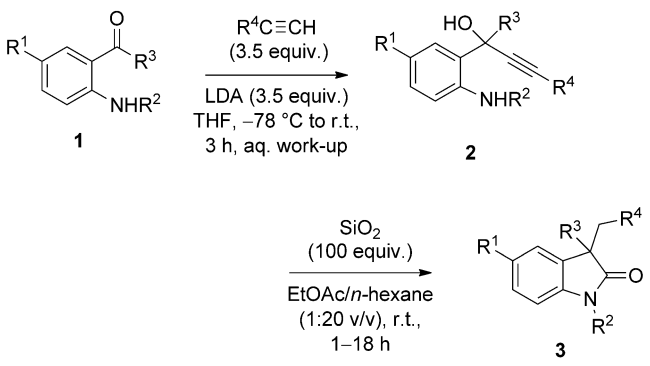
Abstract: 2-Alkylaminophenylprop-1-yn-3-ols, prepared from the lithium diisopropylamide (LDA)-mediated 1,2-addition of alkynes to 1-(2-aminophenyl) ketones, can be converted to 3,3-disubstituted 2-oxindoles by using silica gel in *n*-hexane/ethyl acetate (20:1 v/v) as the reaction medium. The utility of the approach as a potential scale-up strategy for the synthesis of 2-oxindoles was exemplified by the large-scale synthesis of one adduct in excellent yield. The synthetic applicability of this chemistry was also demonstrated by the recycling of the silica gel up to 8 times with no apparent loss of activity being observed for the same example.

Keywords: alkynes; carbonyl compounds; heterogeneous catalysis; 2-oxindoles; silica gel

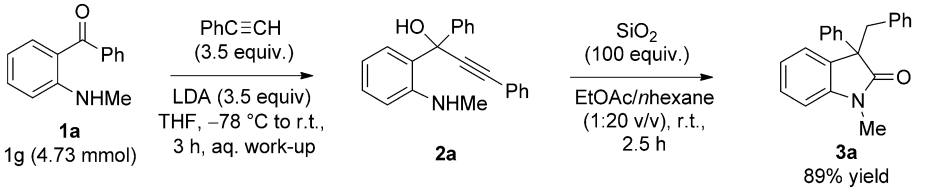
The various chemical and physical properties of silica gel have established it to be an indispensible functional material in chemistry.[1–5] This is reflected by its numerous applications, ranging from its use as the stationary phase in the separation of organic compounds by flash column chromatography[2] to serving as the solid phase support for the metal catalyst in heterogeneous catalysis.[3] In the case of the former activity, the marginally acidic nature of the native form of silica gel, it has a pH value that is close to neutral, can sometimes make the isolation of compounds containing acid-labile functional groups a challenge.[4] On the flip side, harnessing this weak Brønsted acid property can also provide the opportunity to devise new silica gel-mediated functional group transformations to various synthetically valuable products.[5] Herein, we report our discovery of a scalable and recyclable heterogeneous synthetic approach to 3,3-disubstituted 2-oxindoles,[6,7] a structural motif found in a myriad of bioactive natural products,[8] in good to excellent yields (Scheme 1). The nitrogen-containing ring forming process relies on base-mediated 1,2-addition of an alkyne to a 1-(2-aminophenyl) ketone followed by silica gel-catalyzed hydroamination/semipinacol rearrangement[9,10] of the resulting propargylic alcohol.[11,12] Added to this, the reaction features operational simplicity under conditions that do not require the exclusion of air or moisture at room temperature. The synthetic method also tolerates a broad range of functional groups that allows for the efficient and atom-economical assembly of a variety of 2-oxindoles from the readily available substrates.

A demonstrative example is the large-scale addition of phenylacetylene (3.5 equiv.) to 2-(methylamino)-benzophenone **1a** (1 g, 4.73 mmol) in the presence of LDA (3.5 equiv.) shown in Eq. (1) in Table 1. By directly treating a 5% EtOAc/*n*-hexane solution in an open round-bottom flask containing the aqueous worked-up crude mixture of this reaction with silica gel (100 equiv.) under ambient conditions at room temperature for 2.5 h, the 2-oxindole product **3a** was obtained in 89% yield. The structure of the 1,2-addi-



Scheme 1. Synthesis of 2-oxindoles from silica gel-mediated cycloisomerization of 2-alkylaminophenylprop-1-yn-3-ols.

Table 1. Large-scale and recyclable silica gel for cycloisomerization of **2a** to **3a**.[a]



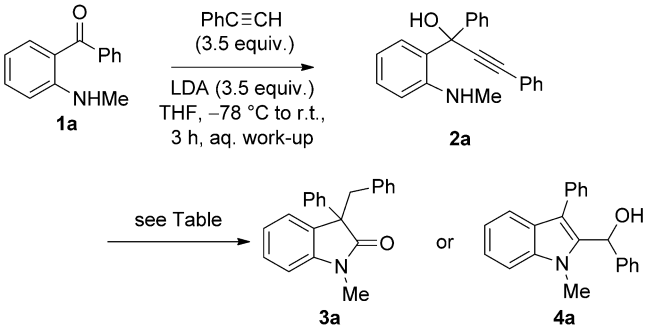
Run	1	2	3	4	5	6	7	8
Yield [%][b]	94 (91)[c,d]	94	94	94	94	90	93	94

[a] All reactions were performed with 0.5 mmol of **1a** and 1.75 mmol of phenylacetylene with 3.5 equiv. of LDA in THF at −78 °C to room temperature for 3 h followed by treatment with 3 g of silica in 10 mL of *n*-hexane/EtOAc (20:1 v/v) at room temperature for 18 h.
[b] Yield determined by ^{1}H NMR with CH_2Br_2 as the internal standard.
[c] Reaction time = 2.5 h.
[d] Value in parenthesis denotes isolated yield.

tion adduct was determined by NMR analysis while that of the nitrogen-containing heterocycle was confirmed by X-ray crystallography.[13] A second illustrative example is the establishment of a recyclable system for the second step of this reaction involving silica gel-mediated cycloisomerization of the 2-alkylaminophenylprop-1-yn-3-ol **2a** (Table 1). Addition of silica gel (100 equiv.) to the aqueous worked-up crude mixture obtained from the base-mediated reaction of 0.5 mmol of **1a** and 3.5 equiv. of phenylacetylene in 5% EtOAc/*n*-hexane, contained in an open round-bottom flask at room temperature for 2.5 h gave **3a** in 91% yield. The silica gel was removed by filtration and used directly for 7 further consecutive transformations under the same above-mentioned conditions. As shown in cycles 2–8, product yields of 90–94% were achieved for each consecutive conversion with no apparent loss of activity observed albeit longer reaction times of 18 h were required for these latter runs.

The discovery of this unprecedented and yet simple 2-oxindole forming process was serendipitously observed during an attempt to purify the crude mixture obtained from LDA-mediated reaction of **1a** with phenylacetylene by silica gel flash column chromatography. Our initial intentions for preparing the 2-alkylaminophenylprop-1-yn-3-ol substrate had been for a study focused on defining the generality of the silver-catalyzed hydroamination of the *N*-protected π-rich alcohols to the corresponding indolin-3-ols.[12b] The unexpected formation of the 2-oxindole product *via* a mechanistically interesting redox rearrangement prompted us to further examine and gain a better understanding of the cycloisomerization process (Table 2). With this in mind, we first surveyed the analogous transformations mediated by other solid acids in place of silica gel (entries 1 and 2). This revealed that a markedly lower product yield of 40% was obtained when the reaction was repeated with

Table 2. Cycloisomerization of **2a** mediated by various acidic reaction conditions.[a]



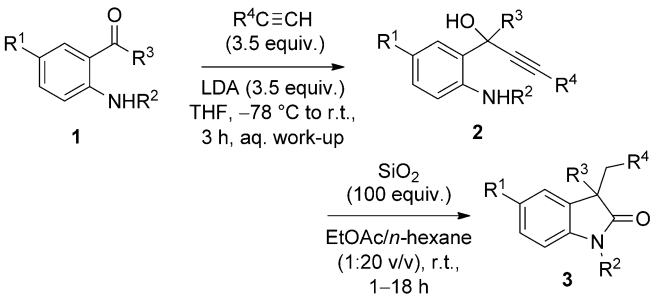
Entry	Acid	Solvent	Yield [%][b]
1	MCM-41	EtOAc/*n*-hexane[c]	40
2	Mont-K10	EtOAc/*n*-hexane[c]	–[d]
3	SiO_2	*n*-hexane	82
4	SiO_2	PhMe	80[e]
5	SiO_2	CH_2Cl_2	90[e]
6	SiO_2	CH_3NO_2	89
7	SiO_2	EtOAc	–[f]
8	SiO_2	acetone	–[f]
9	SiO_2	THF	–[f]
10	*p*-TsOH·H_2O[g]	EtOAc/*n*-hexane[c]	–[h]

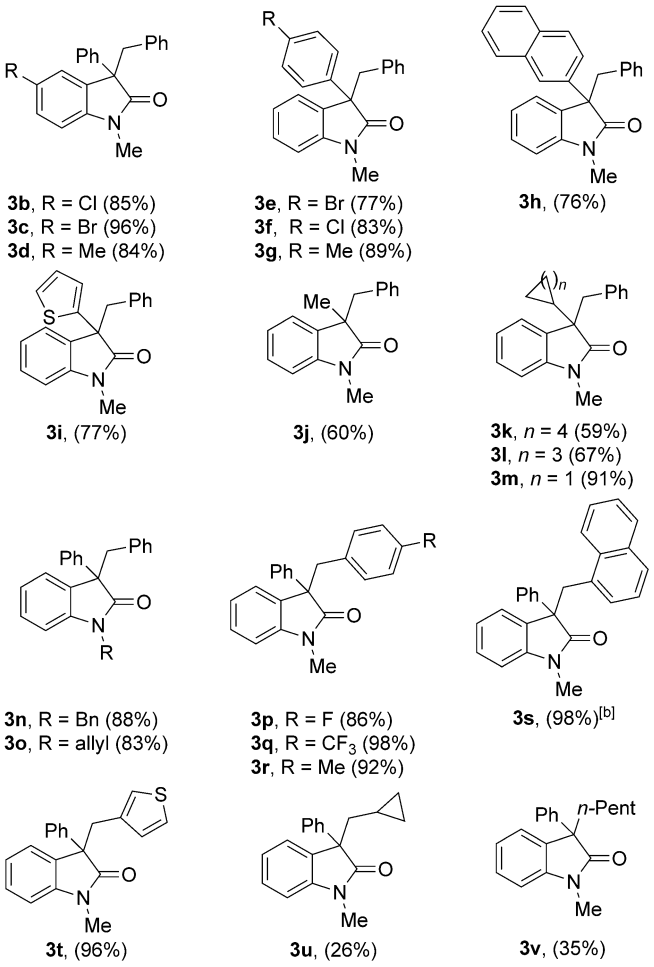
[a] All reactions were performed with 0.5 mmol of **1a** and 1.75 mmol of phenylacetylene with 3.5 equiv. of LDA in THF at −78 °C to room temperature for 3 h followed by the solid acid (3 g) in 10 mL of solvent at room temperature for 24 h.
[b] Yield determined by ^{1}H NMR with CH_2Br_2 as the internal standard.
[c] Ratio of *n*-hexane/EtOAc = 20:1.
[d] Mixture of unknown decomposition products obtained based on ^{1}H NMR and TLC analysis of the crude reaction mixture.
[e] Reaction time = 1 h.
[f] Starting materials recovered in near quantitative yield.
[g] Reaction was performed with 5 mol% of *p*TsOH·H_2O.
[h] Compound **4a** was obtained in 38% yield.

MCM-41 (entry 1).[14] In contrast, the analogous reaction mediated by Mont-K10,[15,16] which has a higher acidity than silica gel,[16c] was found to give a mixture of unidentifiable decomposition products based on TLC and ^{1}H NMR analysis (entry 2). These initial findings led us to surmise that the trigger for the present nitrogen-ring forming process could be due to the mildly acidic conditions provided by silica gel. This was further supported by the outcome of control experiments in other solvents or in the presence of a strong Brønsted acid such as *p*TsOH·H_2O (entries 3–10). Slightly lower product yields of 80–90% were afforded on employing *n*-hexane, toluene, dichloromethane or mildly acidic $MeNO_2$ instead of 5% EtOAc/*n*-hexane as the solvent system (entries 3–6). On the other hand, the propargylic alcohol was only detected by ^{1}H NMR analysis of the crude mixture when polar solvents, such as EtOAc, acetone and THF, were used as the reaction medium (entries 7–9). With 5 mol% of *p*-TsOH·H_2O as the catalyst in 5% EtOAc/*n*-hexane, the reaction was found to furnish the (1*H*-indol-2-yl)methanol **4a** in 38% yield along with a mixture of decomposition products that could not be identified by NMR analysis or mass spectrometry (entry 10).

We next explored the scope of the present 1,2-addition and cycloisomerization reaction with the LDA/silica gel system (Table 3). These experiments showed that a series of 3,3-disubstituted 2-oxindoles could be afforded in good to excellent yields from the corresponding 1-(2-aminophenyl) ketones **1a**–**o** and alkynes. Reactions of 1-(2-aminophenyl) ketones containing an electron-withdrawing (**1b**, **1c**) or electron-donating group (**1d**) on the aniline ring with phenylacetylene were found to proceed well, giving the corresponding 3,3-disubstituted 2-oxindole derivatives in 84–96% yield. The presence of other aryl (**1e–h**), 2-thienyl (**1i**), alkyl (**1j**) or cycloalkyl (**1k**–**m**) motifs at the carbonyl carbon center of the ketone was found to have no influence on the course of the reaction and on treating with phenylacetylene, furnished **3e**–**m** in 59–91% yield. Likewise, 1-(2-aminophenyl) ketones with an *N*-benzyl (**1n**) or *N*-allyl (**1o**) instead of an *N*-methyl protecting group was found to be well tolerated and reaction with phenylacetylene afforded **3n** and **3o** in 88 and 83% yields, respectively. The analogous reactions of **1a** with different alkynes bearing a phenyl group with an electron-donating or electron-withdrawing group at the *para* position or a sterically demanding 1-naphthalenyl, or 3-thienyl moiety were also found to provide the corresponding 2-oxindole adducts **3p**–**3t** in 86–98% yields. The only exceptions were the 1,2-addition/cycloisomerization reactions of **1a** with ethynylcyclopropane or hex-1-yne, which gave **3u** and **3v** in lower yields of 26 and 35%, respectively. The structures of **3g**, **3h**, **3j**, **3p** were determined by X-ray crystal structure measurements.[17]

Table 3. Cycloisomerization of 2-alkylaminophenylprop-1-yn-3-ols **2b**–**v** mediated by silica gel.[a]

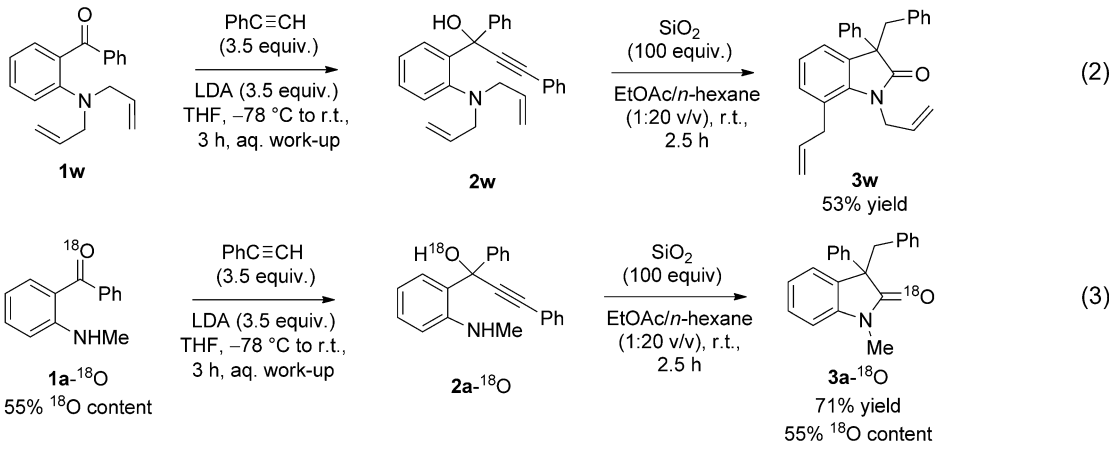




[a] All reactions were performed with 0.5 mmol of **1** and 1.75 mmol of the alkyne with 3.5 equiv. of LDA in THF at −78 °C to room temperature for 3 h followed by silica gel (100 equiv.) in 10 mL of *n*-hexane/EtOAc (20:1 v/v) at room temperature for 1–18 h. Values in parentheses denote isolated product yields.

[b] Reaction conducted at 40 °C for 18 h.

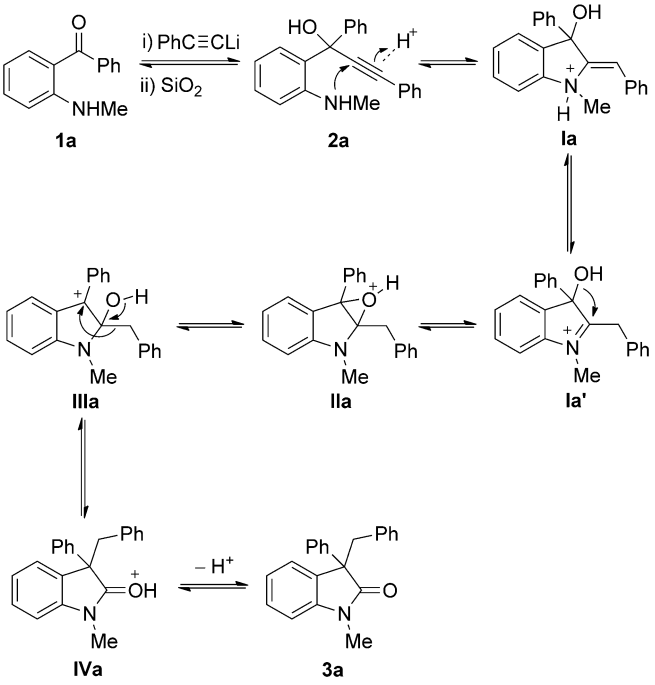
While the above results implicate a cyclization pathway involving hydroamination followed by semipinacol rearrangement, to demonstrate this to be the case, the following control experiments were performed (Scheme 2). As it was anticipated that the



Scheme 2. Control experiments with **1w** and **1a**-^{18}O mediated by silica gel.

propargylic alcohol would lead to the formation of an enammonium cationic species, we reasoned that trapping of this intermediate in an intramolecular manner might be possible on introducing a Michael acceptor, such as an allyl group, as a substituent in the nitrogen center. Thus, we first examined the reaction of *N*,*N*-diallyl-protected ketone **1w** with phenylacetylene under the conditions described in Scheme 2, Eq. (2). This test afforded the 3,3-disubstituted 2-oxindole derivative **3w** in 53% yield and corroboration that formation of the nitrogen-containing ring occurs *via* the posited hydroamination step.[5c,18] In a second control experiment, the LDA-mediated 1,2-addition of phenylacetylene to **1a**-^{18}O with an ^{18}O content of 55% followed by treatment of the resulting crude mixture with 3 g of silica gel in 5% EtOAc/*n*-hexane under the conditions described in Scheme 2, Eq. (3) was investigated. The test reaction gave **3a**-^{18}O in 71% yield and with retention of the ^{18}O content based on LC-MS measurements. This led us to surmise the apparent migration of the carbonyl group in the ketone substrate to the C-2 position in the product to occur in an intramolecular manner. It also hinted that the semipinacol rearrangement of the presumed formed enammonium cationic intermediate proceeds *via* an epoxide adduct.

A tentative mechanism for the present LDA-mediated/silica gel-promoted reaction to form 3,3-disubstituted 2-oxindoles is put forward in Scheme 3. Using the LDA-mediated 1,2-addition of phenylacetylene to **1a** to form the propargylic alcohol **2a** as a representative example, this could initially involve the activation of the alkyne moiety of this newly formed adduct on exposure to silica gel. As a consequence hydroamination involving nucleophilic attack by the pendant alkylamido group in a 5-*exo*-dig manner might occur to produce the cationic enammonium cycloadduct **Ia** and its iminium isomer **Ia′**. This is the active species that undergoes the semipinacol rearrangement process beginning with addition of the alcohol group to the iminium carbon center to give the oxiranium adduct **IIa**. This is followed by formation of a carbocation at the C-3 position to give **IIIa** which, upon oxidative 1,2-migration of the alkyl group from the C-2 to C-3 position, would furnish **IVa**. Subsequent deprotonation of the resultant oxonium species **IVa** would then provide the 2-oxindole product. The lower product yields afforded for reactions with alkyl-substituted alkynes such as ethynylcyclopropane and hex-1-yne would be consistent with the lower ability of the pendant group to stabilize a partial positive charge in



Scheme 3. Proposed mechanism for the silica gel-mediated cycloisomerization of propargylic alcohols represented by **2a**.

the course of the 1,2-migration process. The preferential formation of **4a** when the reaction of **2a** was subjected to *p*-TsOH·H_2O could originate from protonation of the alcohol group in **Ia** that leads to nucleophilic substitution of the resulting activated adduct at the allylic carbon position by H_2O.[19]

In summary, we have developed an efficient and practical two-step method for the synthesis of 3,3-disubstituted 2-oxindoles from base-mediated 1,2-addition of readily available alkynes to ketones followed by silica gel-promoted cycloisomerization of the resulting crude mixture. Achieved under reaction conditions that are tolerant to air and moisture at room temperature, the potential of our approach to the *N*-heterocycle was also exemplified by the large-scale preparation of one example in excellent yield. Added to this is the development of a recycling system that was shown to be effective for up to 8 cycles. This is notable in view of the current need for more rapid and direct atom economical chemical processes that can make use of low cost and readily available substrates and catalytic systems. Efforts exploring the scope and synthetic applications of the present reaction are currently underway and will be reported in due course.

Experimental Section

General Procedure

To a stirred solution of *in situ* formed LDA (3.5 equiv.) in THF (3 mL) at −78 °C was added the appropriate alkyne (1.75 mmol). The resulting reaction mixture was allowed to stir for a further 1 h before the ketone **1** (0.5 mmol) in THF (2 mL) was added to the reaction mixture and stirred for 1 h at the same temperature and at room temperature for 1 h. Upon completion, the reaction mixture was quenched with saturated NH_4Cl (15 mL) and extracted with EtOAc (2× 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture obtained was dissolved with *n*-hexane/EtOAc (10 mL, 20:1 v/v) contained in an open round-bottom flask and silica gel (3 g) was added. The reaction mixture was stirred and monitored by TLC analysis until completion. The reaction mixture was filtered, washed with EtOAc (20 mL), concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc = 10:1) to give the product **3**.

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[18] CCDC 965152 (**3w**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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