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Solid-phase synthesis of isoindolines via a rhodium-catalyzed [2+2+2] cycloaddition

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Abstract—An efficient solid-phase synthesis of isoindolines is reported. The key reaction step is a rhodium-catalyzed [2+2+2] cycloaddition of alkynes to give isoindolines in good yield.

Combinatorial chemistry and parallel synthesis have been applied extensively by medicinal chemists as one approach to the discovery and optimization of lead molecules. While solution phase parallel synthesis is being used more routinely in the laboratory, solid-phase synthesis continues to be an important approach to synthesize combinatorial libraries, especially for heterocyclic compounds requiring multi-step syntheses.[1]

One class of heterocycles, isoindolines, has been shown to elicit a wide array of biological effects including NMDA-receptor antagonism,[2] α1B-adrenergic receptor antagonism,[3] inhibition of amyloid protein aggregation,[4] modulation of estrogen receptors,[5] modulation of dopamine D_3 and D_4 receptors,[6,7] 5-HT_7 receptor antagonism,[8] antibacterial activity,[9] inhibition of nitric oxide synthase,[10] inhibition of selective serotonin reuptake,[11] and modulation of 5-HT_{1A} receptor.[12]

A variety of approaches to synthesize isoindolines in solution phase have been described in the literature.[13–19] To our knowledge, the synthesis of isoindolines on solid phase has not yet been reported. In this paper, we report the first solid-phase synthesis of isoindolines via a rhodium-catalyzed [2+2+2] cycloaddition.[13,20] Grigg et al. have previously applied Wilkinson's catalyst to effect the cycloaddition of various diynes with monoynes to produce several heterocycles in solution phase.[13] In their paper, the authors showed one example containing the isoindoline core, but that example is *N*-acetylated. They also reported that dipropargylamine did not react under their conditions to yield the desired isoindoline. In this paper, we have extended this method to include the use of dipropargylamine in the synthesis of the substituted isoindolines. Moreover, since we attach the dipropargyl amine to the resin, we can use excess reagents to help drive the reaction toward higher yields. Unlike all previous publications, we see no evidence of competing linear dimerization or cyclotrimerization of the substituted acetylenes.

As outlined in Scheme 1, commercially available 4-(4-formyl-3-methoxyphenoxy)-butyrylaminomethylated resin **1** was treated with an excess of benzylamine and sodium triacetoxyborohydride in 1,2-dichloroethane at room temperature overnight. The resulting resin **2** was treated with 8 equiv. of 4-chloromethylbenzoic acid in the presence of 8 equiv. of 1,3-diisopropylcarbodiimide (DIC) and 8 equiv. of 1-hydroxybenzotriazole hydrate (HOBt) in DMF. The mixture was agitated at room temperature overnight to afford resin **3**. *N*-Alkylation of resin **3** with 10 equiv. of dipropargylamine was carried out in the presence of diisopropylethylamine (DIEA) in DMF at 60°C overnight to afford resin **4**. Quality control of resins **3** and **4** was performed by cleavage of the scaffolds from the resins (TFA) and subsequent analysis (LC/MS). In the next step, resin **4** was reacted with various substituted alkynes in the presence of chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) at 80°C in $CHCl_3$/EtOH to form isoindolines through a rhodium-catalyzed [2+2+2] cycloaddition.[21] It should be mentioned that $CHCl_3$/EtOH gave the best result for the cycloaddition among various solvents tried ($CHCl_3$/EtOH, DMSO, DMF, $CHCl_3$). In addition, the amount of Wilkinson's cata-

Keywords: combinatorial chemistry; solid-phase synthesis; isoindolines; [2+2+2] cycloaddition.

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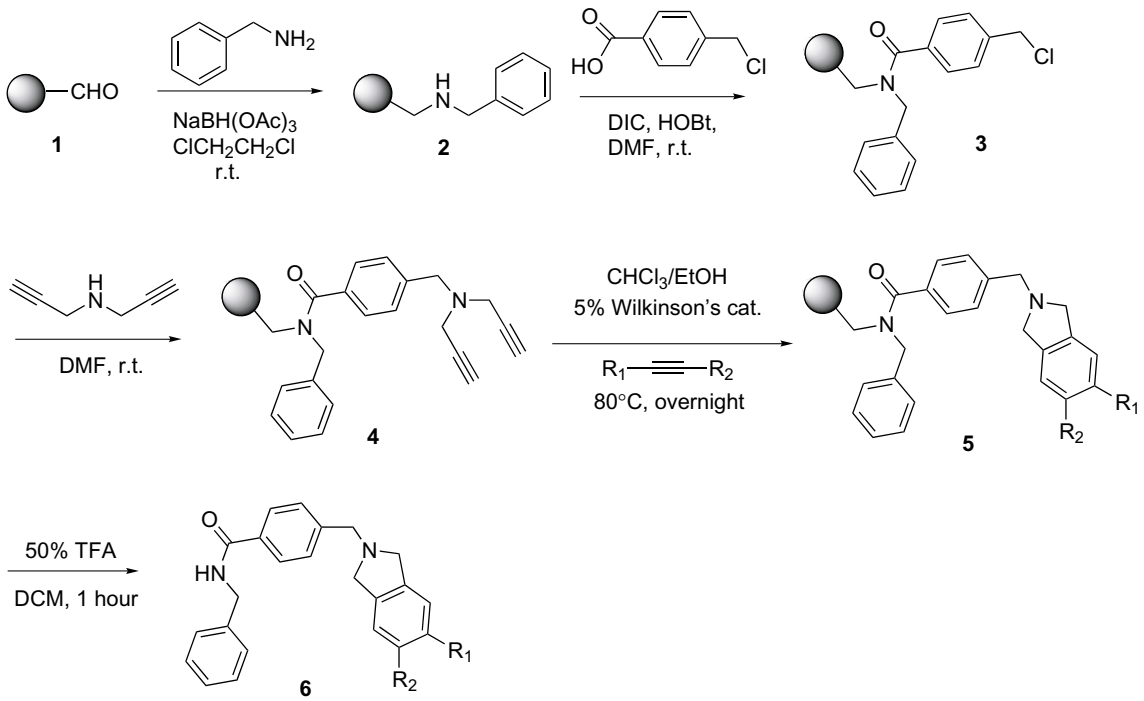
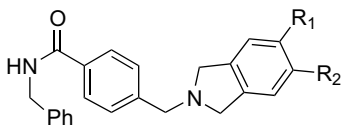
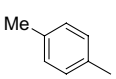


Scheme 1.

lyst used in the cycloaddition was also optimized. While 5, 10, and 20% equiv. of catalyst showed equally good results, 1 and 2.5% equiv. of catalyst gave low yield of products. Therefore, 5% equiv. of catalyst was chosen for all cycloadditions. Finally, products **6** were cleaved from the resin by treatment with TFA. The crude products were purified by flash chromatography to afford the desired isoindoline analogs in 20–85% isolated yield (Table 1). Mono-substituted alkynes gave better yields than di-substituted alkynes, possibly due to steric factors. The purity of the products was determined by RP-HPLC and correct molecular weight was confirmed by mass spectrometry (LC/MS with an electrospray sample inlet system).[22] Structures were further confirmed by ^{1}H and ^{13}C NMR spectroscopy.[23]

Table 1.



Entry	R_1	R_2	Yield (%)[a]
6a	H	CH_2OH	85
6b	H	CH_2OMe	81
6c	H	CH_2NMeBn	68
6d	H	$(CH_2)_5Me$	79
6e	H		62
6f	H	Ph	70
6g	H		83
6h	Me	Ph	20

[a] The isolated yields were based on the initial loading.

In summary, we have developed a novel solid-phase synthesis of isoindolines. The key reaction step is a rhodium-catalyzed cycloaddition of a resin-bound dipropargylamine and various alkynes to form the isoindoline ring system. The resin-bound dipropargylamine could be prepared from dipropargylamine coupled to various resin-bound halides or carboxylic acids. Therefore, a large number of resins and building blocks could be used in this synthesis, which might further increase the structural diversity.

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21. General procedure for the cycloaddition: To resin **4** (1.0 equiv.) in EtOH/$CHCl_3$ (1.25 mL/1.25 mL) was added chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst) (0.05 equiv.) and a substituted alkyne (10.0 equiv.). The mixture was agitated at 80°C overnight. After cooling, the resin was filtered, washed three times with DMF, MeOH and CH_2Cl_2 and dried. Resin **5** was suspended in CH_2Cl_2 (1.0 mL), followed by the addition of TFA (1.0 mL) at room temperature. The mixture was agitated for 1 h at rt. Then the resin was filtered, washed with CH_2Cl_2 (2×2.0 mL) and the filtrate evaporated to afford the crude product, which was purified by silica gel column chromatography (EtOAc to EtOAc/MeOH (10/1)) to give the desired product as a yellow solid in 20–85% yield.
22. LC–MS was performed on an Agilent Series 1100 MSD instrument with an electrospray sample inlet system. HPLC profile generated on an Eclipse XDB-C18 rapid resolution 4.6×50 mm column with a gradient of 85:15–10:90 of 0.1% TFA:acetonitrile with 0.1% TFA and UV detection at 260 nm.
23. Analytical data for isoindoline analogs:
6a: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.47 (br, 1H), 8.05 (d, 2H, J=8.0 Hz), 7.77 (d, 2H, J=8.0 Hz), 7.42 (m, 3H), 7.33 (m, 4H), 7.28 (m, 1H), 4.69 (s, 2H), 4.66 (br, 6H), 4.64 (s, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 166.69, 144.38, 136.63, 135.87, 135.68, 134.10, 131.47, 129.25, 128.76, 128.51, 127.80, 127.72, 123.50, 121.83, 64.20, 58.51, 58.42, 43.97, 41.31; MS (ESI) m/z for $C_{24}H_{24}N_2O_2$ (MH^+): 373.2.
6b: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.39 (br, 1H), 8.02 (d, 2H, J=8.0 Hz), 7.64 (d, 2H, J=8.0 Hz), 7.41 (d, 1H, J=7.2 Hz), 7.40 (s, 1H), 7.35 (d, 1H, J=7.2 Hz), 7.34 (d, 1H, J=7.2 Hz), 7.26 (m, 4H), 4.65 (d, 2H, J=6.0 Hz), 4.44 (s, 2H), 4.30 (br, 2H), 4.27 (m, 4H), 3.34 (s, 3H); MS (ESI) m/z for $C_{25}H_{26}N_2O_2$ (MH^+): 387.2.
6c: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.25 (br, 1H), 7.97 (d, 2H, J=8.0 Hz), 7.53 (d, 2H, J=8.0 Hz), 7.42 (m, 4H), 7.35 (m, 4H), 7.26 (m, 4H), 7.20 (m, 1H), 4.64 (d, 2H, J=6.0 Hz), 3.99 (s, 2H), 3.92 (s, 2H), 3.90 (s, 2H), 3.54 (s, 2H), 3.53 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 167.21, 144.15, 144.54, 140.16, 134.66, 129.68, 129.37, 129.27, 129.10, 128.52, 128.25, 128.23, 127.78, 123.54, 122.78, 66.54, 62.46, 60.35, 59.64, 59.47, 44.03, 42.40; MS (ESI) m/z for $C_{32}H_{33}N_3O$ (MH^+): 476.2.
6d: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.41 (br, 1H), 7.99 (d, 2H, J=8.0 Hz), 7.60 (dd, 2H, J=2.4, 8.0 Hz), 7.39 (d, 1H, J=8.0 Hz), 7.38 (s, 1H), 7.33 (m, 2H), 7.25 (m, 2H), 7.16 (d, 1H, J=8.0 Hz), 7.10 (m, 1H), 4.64 (d, 2H, J=6.0 Hz), 4.24 (m, 2H), 4.18 (m, 4H), 2.60 (dd, 1H, J=7.4, 7.6 Hz), 2.36 (m, 1H), 2.17 (m, 1H), 1.75 (m, 1H), 1.60 (m, 2H), 1.31 (m, 4H), 0.87 (t, 3H, J=6.8 Hz); MS (ESI) m/z for $C_{29}H_{34}N_2O$ (MH^+): 427.3.
6e: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.41 (br, 1H), 8.02 (d, 2H, J=8.0 Hz), 7.73 (d, 2H, J=8.0 Hz), 7.40 (s, 1H), 7.38 (s, 2H), 7.35 (m, 1H), 7.32 (s, 1H), 7.30 (m, 1H), 7.28 (m, 1H), 7.25 (m, 1H), 6.14 (m, 1H), 4.64 (d, 2H, J=6.0 Hz), 4.58 (s, 2H), 4.54 (br, 4H), 2.38 (m, 2H), 2.18 (m, 2H), 1.76 (m, 2H), 1.64 (m, 2H); MS (ESI) m/z for $C_{29}H_{30}N_2O$ (MH^+): 423.2.
6f: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.24 (br, 1H), 7.96 (d, 2H, J=8.0 Hz), 7.63 (dd, 2H, J=2.4, 8.0 Hz), 7.53 (d, 2H, J=8.0 Hz), 7.50 (s, 1H), 7.45 (m, 3H), 7.35 (m, 2H), 7.32 (m, 4H), 7.27 (m, 1H), 4.62 (d, 2H, J=6.0 Hz), 4.00 (s, 2H), 3.97 (s, 2H), 3.95 (s, 2H); MS (ESI) m/z for $C_{29}H_{26}N_2O$ (MH^+): 419.2.
6g: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.41 (br, 1H), 8.03 (d, 2H, J=8.0 Hz), 7.74 (d, 2H, J=8.0 Hz), 7.62 (s, 1H), 7.59 (d, 1H, J=8.0 Hz), 7.53 (d, 2H, J=8.0 Hz), 7.42 (m, 2H), 7.38 (s, 1H), 7.33 (dd, 2H, J=1.6, 7.2 Hz), 7.27 (d, 2H, J=7.2 Hz), 7.24 (m, 1H), 4.63 (m, 8H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 166.85, 142.39, 140.67, 138.49, 138.32, 136.46, 131.34, 130.56, 129.32, 128.84, 128.58, 127.93, 127.88, 127.78, 124.23, 122.07, 58.77, 58.62, 44.06, 40.66, 21.16; MS (ESI) m/z for $C_{30}H_{28}N_2O$ (MH^+): 433.2.
6h: ^{1}H NMR (400 MHz, CD_3COCD_3): δ 8.37 (br, 1H), 8.04 (d, 2H, J=8.0 Hz), 7.76 (d, 2H, J=8.0 Hz), 7.45 (m, 2H), 7.37 (m, 2H), 7.32 (m, 5H), 7.29 (m, 2H), 7.20 (m, 1H), 4.72 (s, 2H), 4.64 (s, 2H), 4.62 (br, 4H), 2.23 (s, 3H); MS (ESI) m/z for $C_{30}H_{28}N_2O$ (MH^+): 433.2.