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Microwave-assisted iridium-catalyzed [2+2+2] cycloaddition of resin-bound dipropargylamine with alkynes

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Abstract—The $[Ir(COD)Cl]_2$/dppe system effectively catalyzes the solid-phase [2+2+2] cycloaddition of resin-bound dipropargylamine with alkynes under microwave conditions. The reaction results in high purity of isoindoline derivatives with moderate yields.

Transition metal-mediated [2+2+2] alkyne cyclotrimerization is a powerful and atom efficient strategy for the convergent synthesis of polysubstituted benzene derivatives.[1] In most cases however, it has been difficult to control the regioselectivity of the intermolecular [2+2+2] cycloaddition and as well as eliminate unwanted oligomeric or self-trimerized products through competing alkyne cycloadditions. A partially intermolecular [2+2+2] alkyne cyclotrimerization is usually utilized to control the selectivity pattern around the arene ring,[2] however; control of both the dimerization and trimerization of diynes and the trimerization of alkynes remains a challenging issue in this chemistry. As an approach for eliminating the formation of self-dimerization and trimerization of diynes, we envisaged that the immobilization of diynes could potentially suppress these side reactions due to the partial site isolation imposed by covalent attachment to the polymer-support.[3]

As part of our continuous interest in microwave-assisted carbocyclizations on solid-support,[4] we were prompted to explore the solid-phase combinatorial synthesis of isoindolines through transition metal-catalyzed [2+2+2] cycloaddition where these competitive pathways could be suppressed by immobilization on solid-support. The isoindoline ring system forms a fundamental part of numerous natural products[5] and represents an underdeveloped area of validated chemical diversity space in which to explore their chemical biology. Structures incorporating this moiety show a wide range of biological properties including platelet aggregation inhibitors and antitumor agents.[6] While the solution-phase synthesis of isoindolines have been described,[7] only a couple of examples using solid-phase synthesis via a rhodium-catalyzed [2+2+2] cycloaddition have been reported.[8] Both of these recently reported solid-supported synthesis suffer from long reaction times (12–48 h) and in particular, isolation of the HCl salt of isoindolines.[8b] The salt form of isoindolines may be a disadvantage when considering compound stability in the long term storage of screening collections[9] or potentially undesirable for biological screening when salts can cause problems with an assay. Herein, we report the first example of the microwave-assisted iridium-catalyzed solid-phase [2+2+2] cycloaddition of resin-bound dipropargylamine with various alkynes, providing an efficient method for the synthesis of salt free isoindoline derivatives in moderate yields.

The required resin-bound dipropargylamine **3** for the cycloaddition was prepared by the reaction of trityl chloride resin **1** (Advanced Chem. Tech, 1% cross linked 1.5 mmol/g) with dipropargyl amine (**2**) using DIEA as the base (Scheme 1). The loading of the reaction was found to be quantitative as evidenced by the nitrogen content present in **3**.[10] The IR spectrum of **3** shows characteristic signal at 3301 and 2120 cm^{-1} due to the presence of alkyne moiety.

Treatment of **3** with **4a** in the presence of $[Ir(COD)Cl]_2$ catalyst and THF as the solvent under microwave

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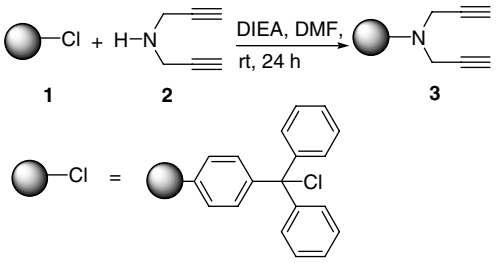
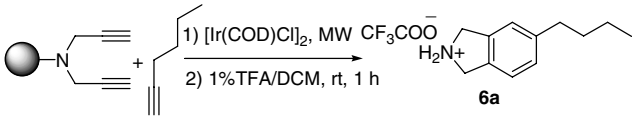
conditions, followed by the resulting resin-bound product with TFA afforded the corresponding TFA salt of isoindolines derivative **6a** in 35% yield. Control experiments revealed that in the absence of iridium catalyst, no reaction occurred.



Scheme 1.

To optimize the solid-supported [2+2+2] cycloaddition, the effects of ligand, solvent, temp., and time were examined (Table 1). From Table 1, it appears that the addition of extra ligand increases the catalytic activity of the reaction (entries 2–5). The addition of diphenylphosphiono ethane (dppe) ligand affords the best yield of cycloadduct **6a** in 65% yield (entry 2). While the use of other bidentate ligands such as dppp and dppb or monodentate ligand, PPh_3 could slightly increase the yield of **6a**, they were less effective than dppe (entries 3–5). A brief examination of different solvents reveal that THF is the solvent of choice (entries 2 and 6–9). Furthermore, the effect of time and temp. studies show little effect on the yield of **6a** (entries 10–15). The same reaction was also carried out utilizing traditional thermal heating (entries 16 and 17). It is noteworthy that the microwave conditions showed a 24-fold shortening of reaction time compared to that of standard thermal heating (entries 2 and 17).

Table 1. Effects of ligand, solvent, temperature and time on the solid-phase [2+2+2] cycloaddition reaction of **3**with 1-hexyne (**4a**), followed by TFA cleavage of resin-bound intermediate **5a**[a]



Entry	Ligand	Solvent	Temperature (°C)	Time (min)	Yield of **6a**[b] (%)
1	—	THF	85	30	35
2	dppe	THF	85	30	65
3	dppp	THF	85	30	45
4	dppb	THF	85	30	53
5	PPh_3	THF	85	30	43
6	dppe	Toluene	85	30	62
7	dppe	DCM	85	30	53
8	dppe	DMF	85	30	51
9	dppe	CH_3CN	85	30	36
10	dppe	THF	60	30	58
11	dppe	THF	110	30	63
12	dppe	THF	135	30	55
13	dppe	THF	85	10	49
14	dppe	THF	85	20	54
15	dppe	THF	85	40	60
16[c]	dppe	THF	85	240	41
17[c]	dppe	THF	85	720	50

[a] Reactions of **3** (0.138 mmol) with 1-hexyne (0.69 mmol) were carried out in the microwave at the specified temp. for the specified time in 2.00 mL of the specified solvent, by using $[Ir(COD)Cl]_2$ (0.0138 mmol) and specified ligand (0.0276 mmol), followed by the cleavage of the resulting resin using 1% TFA/DCM at rt for 1 h.

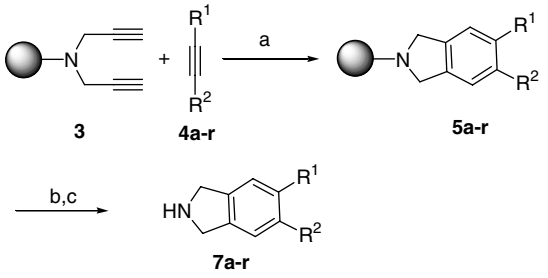
[b] Yields were measured by the ^1H NMR integration method using DMF as an internal standard.

[c] No microwave irradiation was employed.

Most notably, the free base of **7** can be obtained by the catch and release purification of TFA salt using basic alumina.[11] A solution of the TFA salt in 5 mL of DCM was passed through a small plug of basic alumina and washed further with 5 mL of DCM. Then, the desired free base can then be released using 5 mL of 1:1 NH_4OH/NH_3. This basic solution was then washed with DCM and evaporation of the organic layer afforded the pure, free amine isoindoline **7** (Scheme 2).

The results for the microwave [2+2+2] cycloaddition of resin-bound dipropargylamine with various alkynes **4a–r** catalyzed by the $[Ir(COD)Cl]_2$/dppe system, followed by the TFA cleavage and subsequent catch and release purification of TFA salt are compiled in Scheme 2 and Table 2.[11] Several alkyl-substituted alkynes **4a–d** underwent cycloaddition to form the corresponding isoindoline derivatives **7a–d** in moderate yields (entries 1–4). In addition, the reaction was successfully extended to aromatic-substituted alkynes **4e–q** (entries 5–17). The observation that the electron-donating groups on the aromatic ring provide a moderately higher yield than that of aromatics with electron-withdrawing groups indicate little effect of the electronic nature of the aromatic alkynes on yield (entries 9–16). An ortho substituent on arylalkyne does not significantly affect the product yield of the catalytic reaction (entry 9). It is noteworthy that the catalytic reaction tolerates a variety of functional groups such as –OMe, $–NMe_2$, –CN, $–NO_2$, and –CHO on the aromatic ring of the alkynes (entries 9–12 and 14–16). Finally, the reaction with propiolate afforded the corresponding isoindoline **7r** in 60% yield (entry 18).

There are a number of interesting features that are noteworthy from the present microwave-assisted solid-supported [2+2+2] cycloaddition. First, in all cases, the present reaction affords single isoindoline product in



Scheme 2. Reagents and conditions: (a) $[Ir(COD)Cl]_2$, dppe, THF, MW, 85 °C, 30 min; (b) 1% TFA/DCM, rt, 1 h; (c) alumina/NH_4OH.

Table 2. Results of the microwave-assisted solid-phase [2+2+2] cycloaddition of **3** with various alkynes **4a**–**r**, followed by the TFA cleavage and catch-release purification

Entry	Alkyne	Product	R^1	R^2	Yield[a] (%)
1	**4a**	**7a**	H	C_4H_9	63 (99)
2	**4b**	**7b**	H	C_6H_{11}	62 (98)
3	**4c**	**7c**	C_3H_7	C_3H_7	68 (98)
4	**4d**	**7d**	C_2H_5	C_3H_7	65 (99)
5	**4e**	**7e**	Ph	Ph	62 (98)
6	**4f**	**7f**	Me	Ph	70 (99)
7	**4g**	**7g**	C_4H_9	Ph	68 (97)
8	**4h**	**7h**	H	Ph	59 (98)
9	**4i**	**7i**	H	*o*-MeOPh	60 (98)
10	**4j**	**7j**	H	*m*-MeOPh	59 (98)
11	**4k**	**7k**	H	*p*-MeOPh	63 (98)
12	**4l**	**7l**	H	*p*-NMe_2Ph	63 (98)
13	**4m**	**7m**	H	*p*-MePh	60 (99)
14	**4n**	**7n**	H	*p*-NO_2Ph	53 (98)
15	**4o**	**7o**	H	*p*-CNPh	50 (97)
16	**4p**	**7p**	H	*p*-CHOPh	55 (97)
17	**4q**	**7q**	H	3-Thienyl	56 (98)
18	**4r**	**7r**	C_3H_7	CO_2Me	60 (98)

[a] Isolated overall yields were calculated based on the loading of trityl chloride resin (1.5 mmol/g) by the supplier. Values given in parentheses represent purity of products as determined by GC.

moderate yields. Unlike solution-phase chemistry, no product resulting from self-dimerization of the diyne was observed. Second, the self-trimerization product of alkynes can be easily removed from the reaction mixture by simple filtration. Third, we have developed a method to obtain salt-free isoindoline via catch-release purification. Most catch release protocols involve expensive polymer-supported or silica-supported reagents, our approach utilizes relatively inexpensive, commercially available basic alumina. The purification procedure is quite simple, requires no column chromatography and provides the products with extremely high purities. Fourth, the present microwave-assisted reaction shows a marked shorter reaction time (30 min) compared to that of the longer reaction times (48 h) observed in any previously reported solution or solid-phase synthesis of isoindolines.

To conclude, we have demonstrated the first iridium-catalyzed solid-phase [2+2+2] cycloaddition of resin-bound dipropargylamine with various alkynes that is promoted by microwave conditions. The catalytic reaction affords the corresponding isoindoline derivatives in moderate yields. This solid-phase reaction is compatible with several functional groups tested. Further extension of this work to study the regioselectivity of this reaction, prepare a large library of isoindolines, and screen these molecules against various biological targets is currently in progress in our laboratories.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.073.

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10. *Preparation of resin-bound dipropargylamine* **3**: Trityl chloride resin (10.0 g, 15 mmol of Cl) was suspended in DMF (100 mL) and swollen for 1 h. Then, dipropargylamine (6.98 g, 75 mmol) and DIEA (9.68 g, 75 mmol) were added under nitrogen atmosphere. The resulting suspension was shaken on a wrist shaker at rt for 24 h. The resin was filtered, washed successively with DCM (2 × 50 mL),

THF (1 × 50 mL), MeOH (1 × 50 mL), and DCM (1 × 50 mL) and dried under vacuum to constant weight to give 10.9 g resin-bound complex **3** as a pale yellow solid. IR (KBr) 3301, 2120 cm^{-1} (found: N, 2.05 @ 1.5 mmol/g requires N, 1.94).

11. *General procedure for the preparation of isoindolines* **7a**–**r**: To a microwave process vial (10.0 mL), resin **3** (100 mg, 0.138 mmol), $[Ir(COD)Cl]_2$ (0.0138 mmol), dppe (0.0276 mmol) were added and the vial was sealed with an aluminium/teflon crimp top. Then a solution of alkyne **4** (0.69 mmol) in dry THF (2.0 mL) was added under nitrogen atmosphere. The reaction mixture was subjected to microwave irradiation (Biotage Emrys™ Optimizer—300 W maximum power) at 85 °C for 30 min. The reaction mixture was filtered and the resin was washed sequentially with CH_2Cl_2 (2 × 50 mL), THF (1 × 25 mL), MeOH (1 × 25 mL), and CH_2Cl_2 (1 × 25 mL) and dried under vacuum for 1 h to afford resin-bound isoindolines **5a**–**r**. Resin-bound isoindolines **5a**–**r** were suspended in 5 mL of 1% DCM/TFA. The resulting suspension was shaken at rt for 1 h and then filtered through a fritted glass funnel. The filtrate was then passed through a small plug of basic alumina and washed with further 5 mL of DCM and discarded the collected DCM. The organic compound is then generated by washing the basic alumina with 5 mL of 1:1 NH_4 OH/MeOH solution. The aqueous solution was diluted with 10 mL of DCM and washed with 5 mL of water. The organic layer was collected and dried over $MgSO_4$ and filtered. The solvent was removed under vacuum to afford pure isoindolines **7a**–**r**.