Synthesis of *N*-Alkyl-octahydroisoquinolin-1-one-8-carboxamide Libraries Using a Tandem Diels–Alder/Acylation Sequence

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A synthetic sequence was developed in which a diene containing an attached secondary amine was reacted with maleic anhydride to afford the title structures in one step. The reaction involves a Diels–Alder reaction combined with a transacylation reaction of the imide group. A series of six scaffolds was constructed using this methodology. Each scaffold was subsequently reacted with 12 amines to afford a library containing 72 compounds.

Introduction

Domino reactions, in which multiple chemical reactions are carried out in a single step, are attractive tools for library synthesis because they can lead to complex structures quickly and with a minimum of chemical manipulations.[1] In one approach, domino reactions are used to afford scaffolds containing handles for subsequent modification, which leads to focused chemical libraries. The use of a strategy-level carbon–carbon bond forming reaction, such as the Diels–Alder cycloaddition, is attractive for library synthesis because of its well-known scope and ability to lead to cyclic materials containing multiple stereocenters.[2] In this paper, we introduce a method that combines the Diels–Alder reaction with an imide acylation reaction to afford octahydroisoquinol-1-one-8-carboxylic acids. The utility of this sequence was demonstrated by the synthesis of a small solution phase focused library of 72 compounds.

Our own interest is primarily in the synthesis of heterocyclic libraries having potential biological activity.[3] In considering ways of adapting the classical Diels–Alder reaction for this purpose, we formulated the reaction of maleic anhydride with an amine-containing diene as shown in Scheme 1. In this scenario, the Alder endo rule would result in the amine-containing side chain emerging cis to a reactive carbonyl group. If conditions could be found to promote both the Diels–Alder and the acylation step, a one-step synthesis of an isoquinolone containing a carboxylic acid for easy diversification would result. Somewhat surprising to us, Diels–Alder sequences that afford isoquinolones are rare; much work in this area has focused on intramolecular versions in which the diene and dienophiles are attached prior to cycloaddition.[4] We felt that the advantages of the approach shown would include the use of an extremely reactive dienophile, the ability to form the C–N bond without a separate alkylation event, and the availability of an emergent carboxylic acid for downstream manipulation.

Methodology Development and Scaffold Synthesis. Our work began with the synthesis of the aminodiene components from 3,5-hexadien-1-ol, which is readily synthesized from ethyl sorbate by deconjugation and reduction.[5] Mesylation and subsequent displacement with a primary amine[6] readily afforded the desired aminodienes in reasonable overall yields and on a 1–2 g scale (Table 1). The displacement of mesylate by the amine was facilitated by microwave irradiation (acetonitrile, 130 °C, 1 h). The amines were purified by silica gel chromatography prior to use in the next step.

The thermal reactions of dienes **1***{1–6}* and maleic anhydride were initially studied (Scheme 2). Again, the high internal pressures and temperatures associated with microwave irradiation facilitated the overall process. Thus, **1***{1–6}* and maleic anhydride were combined in a 5 mL microwave vial in dichloroethane (DCE) and heated to 165 °C. After ca. 1.5 h, maximum yields of the isoquinolones **2***{1–6}* were obtained. A survey of reaction conditions showed that the best yields were obtained using 1.25 equiv of the dieneophile relative to the diene **1***{1–6}*. We briefly examined a few additional solvents (CH_2Cl_2, toluene, CH_3CN), but only dichloroethane afforded good conversion in this reaction. In addition, the relatively high temperatures and ca. 1.5 h reaction times were also found to be necessary for optimal yields.

In this reaction, no intermediates were detected under normal conditions, leaving the question of mechanism open. Although we originally considered the reaction to proceed by first undergoing the Diels–Alder reaction and only then undergoing intramolecular acylation (route a), it would be imprudent to completely rule out the other order of reactions (route b). For example, related intramolecular Diels–Alder reactions are certainly known[4] and there is evidence that the product of maleic anhydride acylation retains cis stereochemistry under thermal condi-

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Scheme 1

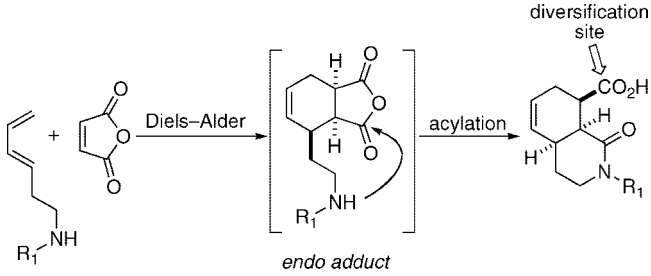
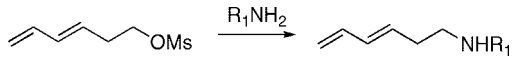
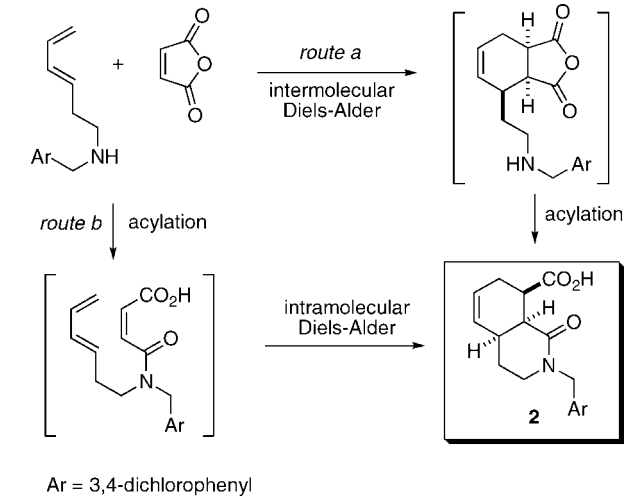


Table 1. Synthesis of the 1-Amino-3,5-hexadienes **1***{1–6}*



entry	R_1	compd	yield (%)
1	*n*-butyl	**1***{1}*	87
2	cyclopropyl	**1***{2}*	40
3	cyclohexyl	**1***{3}*	78
4	benzyl	**1***{4}*	92
5	3,4-dichlorobenzyl	**1***{5}*	97
6	3,4-dimethoxybenzyl	**1***{6}*	80

Scheme 2

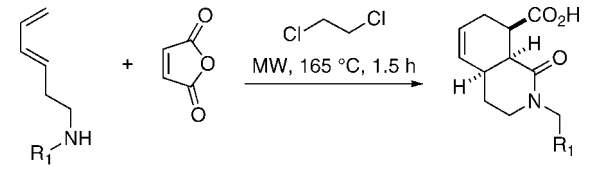


tions.[7] When the reaction was carried out to less than full conversion, only starting materials and the product **2** were evident by thin layer chromatography.

Having settled upon standard conditions, the dienes were reacted with maleic anhydride to afford a series of six isoquinol-1-ones (Table 2). All of the reactions shown gave isoquinolones in good yields and, when carried out on scale, in ca. 0.5–1.5 g quantities. Some of the products were not readily isolated by standard silica chromatography but could be nicely purified using a buffered ether eluent previously exploited by Taber and coworkers for the purification of carboxylic acids.[8]

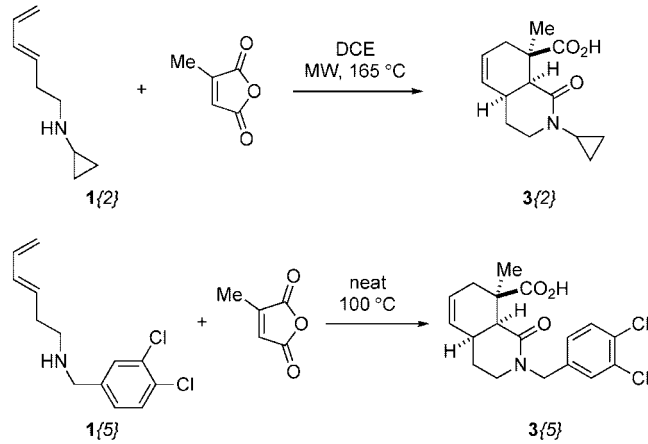
Two additional dienophiles afforded useful cycloaddition products. The reaction of aminodiene **1***{2}* with citraconic anhydride under the above optimized conditions afforded the methyl isoquinolone product **3***{2}* in 54% yield in a solitary trial (Scheme 3). In addition, the reaction of aminodiene **1***{5}* and citraconic anhydride at 100 °C thermal heating for 5.5 hours without solvent gave the isoquinolone product **3***{5}* in 76% yield (Scheme 3). Finally, dimethyl fumarate was reacted with **1***{5}* and found to give compounds **4a** and **4b**,

Table 2. Diels–Alder Reactions of Dienes **1***{1–6}* with Maleic Anhydride

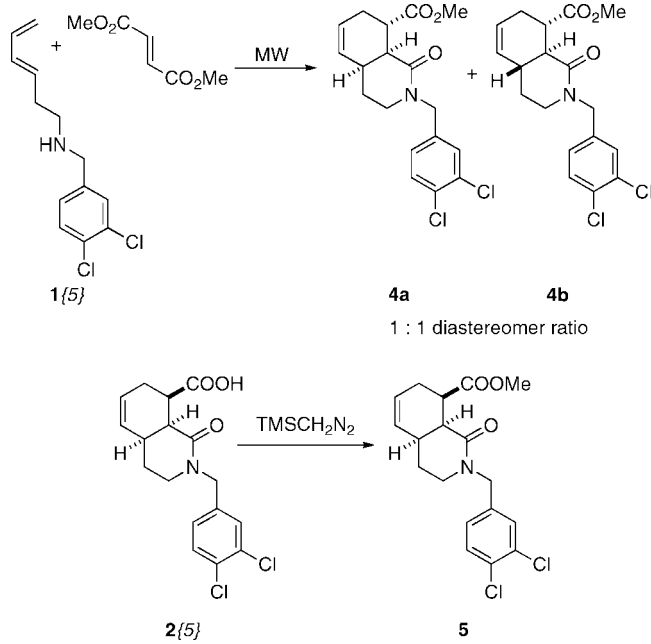


entry	diene	R_1	product	yield (%)
1	**1***{1}*	*n*-butyl	**2***{1}*	74
2	**1***{2}*	cyclopropyl	**2***{2}*	76
3	**1***{3}*	cyclohexyl	**2***{3}*	68
4	**1***{4}*	benzyl	**2***{4}*	74
5	**1***{5}*	3,4-dichlorobenzyl	**2***{5}*	80
6	**1***{6}*	3,4-dimethoxybenzyl	**2***{6}*	80

Scheme 3



Scheme 4



as an equimolar mixture of isomers, in 68–76% combined yield (Scheme 4). Treatment of adduct **2***{5}* with (trimethylsilyl)diazomethane smoothly afforded the ester **5**, which was shown to be isomerically distinct from **4a** and **4b** (Scheme 4), demonstrating that both Diels–Alder reactions were stereoselective.

Table 3. Parallel Synthesis of a 72-Member Quinolone Amide Library

product	quinolone scaffold	amine	crude purity (%)	purified yield (mg)	final purity (%)	HRMS, calcd for $[M + H]^+$	HRMS, found
7*{1}*	**2***{1}*	**6***{1}*	97	26 (82%)	100	321.2178	321.2186
7*{2}*	**2***{1}*	**6***{2}*	88	35 (88%)	100	396.2651	396.2655
7*{3}*	**2***{1}*	**6***{3}*	86	31 (88%)	91	355.2386	355.2395
7*{4}*	**2***{1}*	**6***{4}*	91	21 (68%)	100	307.2386	307.2399
7*{5}*	**2***{1}*	**6***{5}*	93	21 (62%)	100	333.2542	333.2568
7*{6}*	**2***{1}*	**6***{6}*	84	31 (85%)	100	371.2335	371.2359
7*{7}*	**2***{1}*	**6***{7}*	93	11 (31%)	100	342.2182	342.2205
7*{8}*	**2***{1}*	**6***{8}*	91	28 (84%)	98	334.1589	334.1610
7*{9}*	**2***{1}*	**6***{9}*	84	25 (78%)	100	327.2073	327.2091
7*{10}*	**2***{1}*	**6***{10}*	81	31 (87%)	100	357.2178	357.2211
7*{11}*	**2***{1}*	**6***{11}*	60	29 (73%)	100	395.1293	395.1315
7*{12}*	**2***{1}*	**6***{12}*	71	32 (75%)	99	429.1557	429.1585
7*{13}*	**2***{2}*	**6***{1}*	80	18 (60%)[a]	87[a]	305.1865	305.1884
7*{14}*	**2***{2}*	**6***{2}*	79	26 (69%)	91	380.2338	380.2351
7*{15}*	**2***{2}*	**6***{3}*	84	17 (50%)	97	339.2073	339.2079
7*{16}*	**2***{2}*	**6***{4}*	89	20 (67%)	100	291.2073	291.2088
7*{17}*	**2***{2}*	**6***{5}*	10	1 (6%)	100	317.2229	317.2252
7*{18}*	**2***{2}*	**6***{6}*	97	22 (61%)	97	355.2022	355.2034
7*{19}*	**2***{2}*	**6***{7}*	84	2 (7%)	100	326.1869	326.1887
7*{20}*	**2***{2}*	**6***{8}*	54	18 (57%)	99	318.1276	318.1291
7*{21}*	**2***{2}*	**6***{9}*	85	13 (42%)	100	311.1760	311.1784
7*{22}*	**2***{2}*	**6***{10}*	74	19 (56%)	100	341.1865	341.1890
7*{23}*	**2***{2}*	**6***{11}*	50	21 (56%)	99	379.0980	379.0995
7*{24}*	**2***{2}*	**6***{12}*	57	29 (70%)	100	413.1244	413.1268
7*{25}*	**2***{3}*	**6***{1}*	95	18 (53%)	100	347.2335	347.2345
7*{26}*	**2***{3}*	**6***{2}*	89	28 (65%)	99	422.2808	422.2815
7*{27}*	**2***{3}*	**6***{3}*	88	24 (63%)	99	381.2542	381.2547
7*{28}*	**2***{3}*	**6***{4}*	91	14 (42%)	100	333.2542	333.2550
7*{29}*	**2***{3}*	**6***{5}*	85	30 (83%)	96	359.2699	359.2714
7*{30}*	**2***{3}*	**6***{6}*	65	36 (90%)	98	397.2491	397.2509
7*{31}*	**2***{3}*	**6***{7}*	99	18 (50%)	95	368.2338	368.2372
7*{32}*	**2***{3}*	**6***{8}*	77	20 (56%)	95	360.1746	360.1762
7*{33}*	**2***{3}*	**6***{9}*	86	24 (69%)	98	353.2229	353.2241
7*{34}*	**2***{3}*	**6***{10}*	65	30 (78%)	98	383.2335	383.2347
7*{35}*	**2***{3}*	**6***{11}*	49	22 (51%)	100	421.1450	421.1469
7*{36}*	**2***{3}*	**6***{12}*	69	32 (69%)	99	455.1713	455.1721
7*{37}*	**2***{4}*	**6***{1}*	89	21 (59%)	100	355.2022	355.2035
7*{38}*	**2***{4}*	**6***{2}*	87	31 (72%)	97	430.2495	430.2491
7*{39}*	**2***{4}*	**6***{3}*	88	29 (75%)	96	389.2229	389.2237
7*{40}*	**2***{4}*	**6***{4}*	82	14 (42%)	98	341.2229	341.2236
7*{41}*	**2***{4}*	**6***{5}*	65	30 (81%)	100	367.2386	367.2401
7*{42}*	**2***{4}*	**6***{6}*	76	39 (96%)	99	405.2178	405.2204
7*{43}*	**2***{4}*	**6***{7}*	99	20 (54%)	97	376.2025	376.2053
7*{44}*	**2***{4}*	**6***{8}*	97	32 (90%)	99	368.1433	368.1456
7*{45}*	**2***{4}*	**6***{9}*	91	34 (93%)	100	361.1916	361.1924
7*{46}*	**2***{4}*	**6***{10}*	87	35 (85%)	100	391.2022	391.2031
7*{47}*	**2***{4}*	**6***{11}*	28	11 (26%)	100	429.1137	429.1150
7*{48}*	**2***{4}*	**6***{12}*	72	45 (99%)	100	463.1400	463.1426
7*{49}*	**2***{5}*	**6***{1}*	98	21 (48%)	100	423.1242	423.1257
7*{50}*	**2***{5}*	**6***{2}*	84	29 (58%)	99	498.1715	498.1718
7*{51}*	**2***{5}*	**6***{3}*	82	23 (49%)	99	457.1450	457.1463
7*{52}*	**2***{5}*	**6***{4}*	90	22 (54%)	100	409.1450	409.1454
7*{53}*	**2***{5}*	**6***{5}*	98	24 (55%)	100	435.1606	435.1616
7*{54}*	**2***{5}*	**6***{6}*	79	44 (92%)	100	473.1399	473.1407
7*{55}*	**2***{5}*	**6***{7}*	98	27 (61%)	99	444.1246	444.1255
7*{56}*	**2***{5}*	**6***{8}*	90	11 (24%)	100	436.0653	436.0671
7*{57}*	**2***{5}*	**6***{9}*	91	33 (77%)	100	429.1137	429.1152
7*{58}*	**2***{5}*	**6***{10}*	84	35 (75%)	100	459.1242	459.1247
7*{59}*	**2***{5}*	**6***{11}*	32	2 (5%)	98	497.0357	497.0356
7*{60}*	**2***{5}*	**6***{12}*	77	44 (82%)	100	531.0621	531.0616
7*{61}*	**2***{6}*	**6***{1}*	85	20 (48%)	100	415.2233	415.2246
7*{62}*	**2***{6}*	**6***{2}*	66	33 (67%)	83	490.2706	490.2709
7*{63}*	**2***{6}*	**6***{3}*	74	23 (51%)	100	449.2440	449.2453
7*{64}*	**2***{6}*	**6***{4}*	76	13 (34%)	100	401.2440	401.2445
7*{65}*	**2***{6}*	**6***{5}*	86	13 (31%)	100	427.2597	427.2602
7*{66}*	**2***{6}*	**6***{6}*	66	23 (49%)	99	465.2389	465.2394
7*{67}*	**2***{6}*	**6***{7}*	92	12 (28%)	99	436.2236	436.2261
7*{68}*	**2***{6}*	**6***{8}*	69	16 (37%)	97	428.1644	428.1667
7*{69}*	**2***{6}*	**6***{9}*	75	16 (39%)	100	421.2127	421.2134
7*{70}*	**2***{6}*	**6***{10}*	70	27 (64%)	100	451.2233	451.2248
7*{71}*	**2***{6}*	**6***{11}*	40	19 (39%)	97	489.1348	489.1344
7*{72}*	**2***{6}*	**6***{12}*	58	32 (61%)	99	523.1611	523.1611

[a] Insoluble sample, purified by flash chromatography.

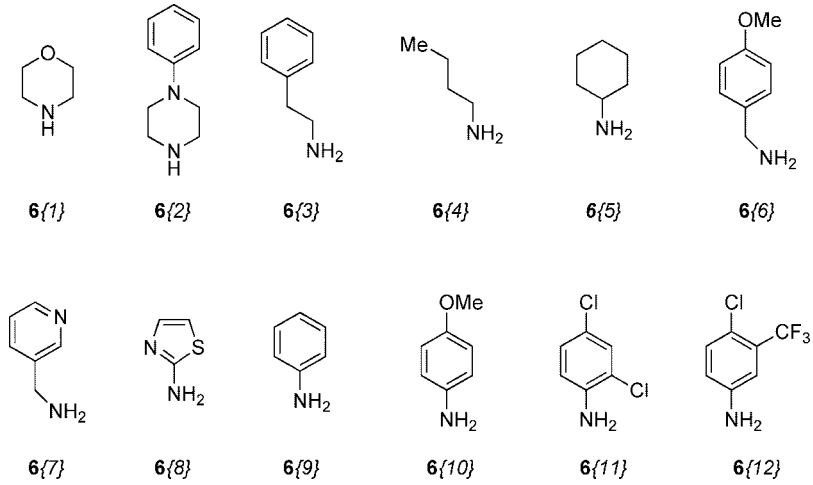
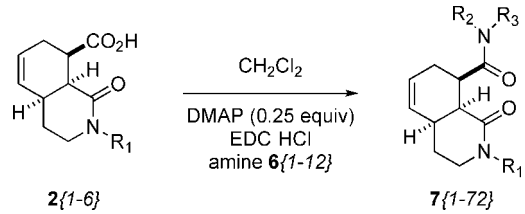


Figure 1. Amines used in library construction.

Scheme 5



Our attempts to carry out the reaction with other dienophiles were disappointing. Thus, all attempts to replace maleic anhydride with *N*-phenyl maleimide or other substituted maleic anhydrides using the conditions noted above only resulting in starting material recovery. The use of various Lewis acids with those dienophiles was also not forthcoming.

Library Synthesis. As a preliminary demonstration of the utility of this method for parallel synthesis, the six scaffolds prepared in quantity **2***{1–6}* were subjected to an additional diversity step. Thus, the acids were reacted with the 12 amines ***6{1–12}*** shown in Figure 1 using a catalytic amount of DMAP and *N*-(3′-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDC·HCl) as the primary coupling reagent (Scheme 5). The amine components were chosen to demonstrate the productive coupling of the quinolone scaffolds over a range of amines with diverse chemical reactivity. The reactions were stirred at room temperature for 14 h then partitioned between CH_2Cl_2 and water in phase separator tubes fitted with hydrophobic filters. The organic layers obtained were directly subjected to solid phase extraction (SPE). Elution with CH_2Cl_2:acetone (1:1) provided the crude amide-coupled products. The compounds thus prepared were subjected to mass-directed HPLC purification to afford the adducts shown (Table 3).

Summary

A Diels–Alder/acylation method (or vice versa) for the synthesis of substituted isoquinol-1-ones-8-carboxylic acids from amine-substituted dienes has been applied to the synthesis of a 72-member amide library. Further work in this area will concentrate on broadening the scope of the one-pot isoquinolone synthesis and streamlining this step for use in library development.

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Supporting Information Available. Experimental details and full characterization data for the synthesis of the carboxylic acid scaffolds **2***{1-6}*, **3***{2, 5}*, **4a/b**, **5**, and the amino dienes **1***{1–3,5–6}* HPLC purification data for all library compounds and ^1H and ^{13}C NMR spectra for 20 representative compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) For recent general reviews of domino reactions, see: *Domino Reactions in Organic Synthesis*; Tietze, L. F., Bräsche, G., Gericke, K. M., Eds.; Wiley: Weinheim, Germany, 2007. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634. (d) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

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