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Phosphine-catalyzed [3+2] cycloaddition of ethyl buta-2,3-dienoate to adamantane-containing N-substituted maleimides

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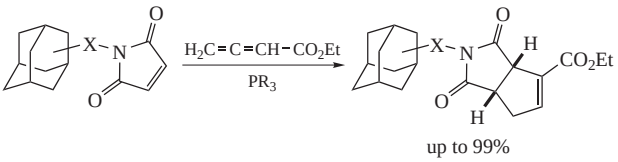
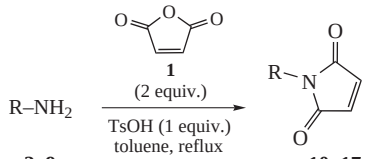
Triphenylphosphine-catalyzed [3+2] cycloaddition between ethyl buta-2,3-dienoate and adamantane-containing N-substituted maleimides affords substituted bicyclic succinimides in excellent yields.

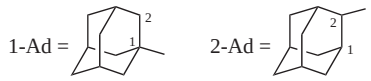


Cycloaddition reactions catalyzed by phosphines are of permanent interest as they provide various carbocyclic and heterocyclic compounds with chiral centers.[1–3] Cycloaddition of allenes with compounds possessing activated carbon–carbon and carbon–heteroatom bonds gives an access to various substituted five-membered carbocycles[4–6] and five- or six-membered heterocycles.[7–9] Maleimides have been intensively studied in such reactions as they can be easily transformed into substituted succinimeds due to the presence of activated double bond.[10] Bicyclic and polycyclic molecules of various architectures were successfully obtained in the phosphine-catalyzed reactions of maleimides.[11–14] The phosphine-catalyzed cycloaddition of maleimides proceeds under mild conditions[15] and affords compounds possessing fragments that occur in natural products with antitumor activity.[16] Some cycloaddition reactions with maleimides are catalyzed by simple phosphines, first of all by triphenylphosphine, while others are carried out in the presence of chiral phosphines, sometimes of a sophisticated structure, to provide high enantioselectivity.[12] On the other hand, compounds containing a lipophilic adamantane moiety show high and versatile biological activity.[17] For this reason, in the present work we synthesized a series of N-substituted maleimides bearing adamantane fragment and subjected them to phosphine-catalyzed [3+2] cycloaddition with ethyl buta-2,3-dienoate as an activated allene.

To obtain substituted maleimides from adamantane-containing amines, first we improved the known procedure[18] for modification of maleic anhydride **1** using more reactive benzylamine **2** and *p*-toluidine **3** which do not contain a bulky adamantyl moiety. The reactions were carried out in boiling toluene in the presence of 1 equiv. of TsOH to ensure higher yields of the products, the reaction time was substantially increased, and 2 equiv. of maleic anhydride **1** were applied (Scheme 1).† Such improvements provided 56% yield of the *N*-benzylmaleimide **10** and 83% yield of *N*-(*p*-tolyl)maleimide **11**. This optimized procedure was extended to obtain a series of new adamantane-containing maleimides in yields from moderate to good. The outcome of the reaction was not directly governed by the bulkiness of the



Amine	R	Product	Yield (%)
2	$PhCH_2$	**10**	56
3	4-MeC_6H_4	**11**	83
4	1-Ad-1,4-C_6H_4	**12**	66
5	1-Ad-CH_2	**13**	53
6	1-Ad-CH_2CH_2	**14**	37
7	1-Ad-OCH_2CH_2	**15**	44
8	2-Ad-CH_2	**16**	40
9	2-Ad-CH_2CH_2	**17**	46



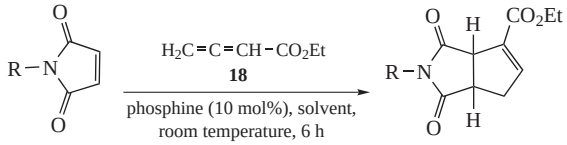
Scheme 1

Synthesis of adamantane-containing maleimides (general procedure). A round bottom flask equipped with a magnetic stirrer and condenser was charged with maleic anhydride (490 mg, 5 mmol) and absolute toluene (10 ml). Then amine (5 mmol) was slowly added to the stirred solution. The mixture was stirred at room temperature for 1 h. Then another portion of maleic anhydride (490 mg, 5 mmol) and *p*-toluenesulfonic acid (860 mg, 5 mmol) were added to the flask and the mixture was refluxed with Dean–Stark trap for 10 h. The mixture was cooled, diluted with ethyl acetate (50 ml), washed with saturated sodium bicarbonate solution, and the water phase was extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, the solvent was evaporated *in vacuo*, and the residue was chromatographed [silica gel, light petroleum, light petroleum–CH_2Cl_2 (2:1 to 1:2)]. Spectral data of compounds **10** and **11** are identical to reported ones.[24,25]

† Amines **4** and **7** were obtained according to reported procedures.[19,20] Amine **5** was synthesized using a described method.[21] Amines **6**, **8** and **9** were obtained according to a reported synthetic procedure.[22] High resolution mass spectrum (HRMS) of compound **22** was measured on a Bruker maXis instrument using electrospray ionization (ESI) under the conditions mentioned in ref. 23.

substituents at the amino group. The use of the adamantylalkyl amines **5**–**9** provided 37–53% yields of the corresponding derivatives **13**–**17**, while the reaction with 4-adamantylaniline **4** gave product **12** in 56% yield.

Optimization of the cycloaddition stage with ethyl buta-2,3-dienoate **18** was studied using maleimides **10** and **11** (Scheme 2). The reaction with **10** was carried out in toluene in the presence of PPh_3 as a catalyst. Variation of the catalyst amount in the range from 5 to 20 mol% caused the change in the reaction time from 10 to 3 h, respectively, to provide total conversion of the starting maleimide **1**. The best yield (98%) of the cycloaddition product **19** was achieved after 6 h in the presence of 10 mol% catalyst.‡ Longer reaction time resulted in undesirable reactions involving the product and allene taken in excess. For the sake of the further investigations of such reactions in the asymmetric version, we tested *rac*-BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthalene] in this process. The reaction with *rac*-BINAP in toluene did not proceed, however, moving to toluene–$CHCl_3$ (1:1) mixture allowed us to obtain product **19** in the same 98%



10–**17** **19**–**26**

Maleimide	Phosphine	Solvent	Product	Yield (%)
10	PPh_3	toluene	**19**	98
	rac-BINAP	toluene–$CHCl_3$		98
11	PPh_3	toluene	**20**	97
	rac-BINAP	toluene–$CHCl_3$		50
12	PPh_3	toluene	**21**	98
	rac-BINAP	toluene–$CHCl_3$		26
13	PPh_3	toluene	**22**	99
	rac-BINAP	toluene–$CHCl_3$		51
14	PPh_3	toluene	**23**	99
15	PPh_3	toluene	**24**	92
16	PPh_3	toluene	**25**	95
17	PPh_3	toluene	**26**	99

Scheme 2

yield. In the case of maleimide derivative **11**, the reaction catalyzed by PPh_3 in toluene afforded the cycloaddition product **20** in 97% yield while *rac*-BINAP in toluene–$CHCl_3$ (1:1) was less productive giving only 50% yield. Other reactions with adamantane-containing maleimides **12**–**17** were conducted using PPh_3 (10 mol%) in toluene, and after 6 h the reactions were complete and the yields of products **21**–**26** reached 92–99% (see Scheme 2). We also tried the reactions with maleimides **12** and **13** using *rac*-BINAP in toluene–$CHCl_3$ (1:1), and achieved much

*1-[4-(1-Adamantyl)phenyl]-1*H*-pyrrole-2,5-dione* **12** was obtained from maleic anhydride (980 mg, 10 mmol) and amine **4** (1135 mg, 5 mmol) in the presence of TsOH (860 mg, 5 mmol). Eluent: light petroleum–CH_2Cl_2 (2:1), yield 1.013 g (66%), yellow crystalline powder, mp 242–243 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.73–1.81 (m, 6H), 1.91–1.92 (m, 6H), 2.10 (br.s, 3H), 6.84 (s, 2H), 7.26 (d, 2H, *J* 8.7 Hz), 7.46 (d, 2H, *J* 8.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.8 (3C), 36.2 (1C), 36.7 (3C), 43.0 (3C), 125.6 (2C), 125.8 (2C), 128.4 (1C), 134.1 (2C), 151.2 (1C), 169.7 (2C). Found (%): C, 78.05; H, 7.13: N, 4.57. Calc. for $C_{20}H_{21}NO_2$ (%): C, 78.15; H, 6.89; N, 4.56.

*1-(1-Adamantylmethyl)-1*H*-pyrrole-2,5-dione* **13** was obtained from maleic anhydride (980 mg, 10 mmol) and amine **5** (825 mg, 5 mmol) in the presence of TsOH (860 mg, 5 mmol). Eluent: light petroleum–CH_2Cl_2 (2:1), yield 649 mg (53%), white crystalline powder, mp 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43–1.44 (m, 6H), 1.53–1.65 (m, 6H), 1.91 (br.s, 3H), 3.15 (s, 2H), 6.67 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 28.1 (3C), 35.0 (1C), 36.6 (3C), 40.5 (3C), 49.5 (1C), 133.8 (2C), 171.4 (2C). Found (%): C, 73.77; H, 8.07; N, 5.64. Calc. for $C_{15}H_{19}NO_2$ (%): C, 73.44; H, 7.81; N, 5.71.

*1-(2-Adamantylmethyl)-1*H*-pyrrole-2,5-dione* **16** was obtained from maleic anhydride (980 mg, 10 mmol) and amine **8** (825 mg, 5 mmol) in the presence of TsOH (860 mg, 5 mmol). Eluent: light petroleum–CH_2Cl_2 (2:1), yield 490 mg (40%), white crystalline powder, mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52–1.55 (m, 2H), 1.64–1.85 (m, 10H), 1.99–2.06 (m, 3H), 3.63 (d, 2H, *J* 8.0 Hz), 6.67 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 27.8 (1C), 28.0 (1C), 29.8 (2C), 31.4 (2C), 38.0 (1C), 38.6 (2C), 40.8 (1C), 42.8 (1C), 133.9 (2C), 171.1 (2C). Found (%): C, 73.36; H, 7.89; N, 5.72. Calc. for $C_{15}H_{19}NO_2$ (%): C, 73.44; H, 7.81; N, 5.71.

For characteristics of compounds **14**, **15** and **17**, see Online Supplementary Materials.

‡ *Phosphine-catalyzed [3 + 2] cycloaddition of maleimides with ethyl buta-2,3-dienoate (general procedure).* A Schlenk tube equipped with magnetic stirrer was charged with phosphine (10 mol%), maleimide (0.3 mmol) and filled with dry argon. Then absolute toluene (2 ml) and allene **18** (67 mg, 0.6 mmol) were syringed through septum. The mixture was stirred at room temperature for 6 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed [silica gel, light petroleum, light petroleum–CH_2Cl_2 (1:1 to 1:2), CH_2Cl_2, CH_2Cl_2–MeOH (250:1 to 50:1)].

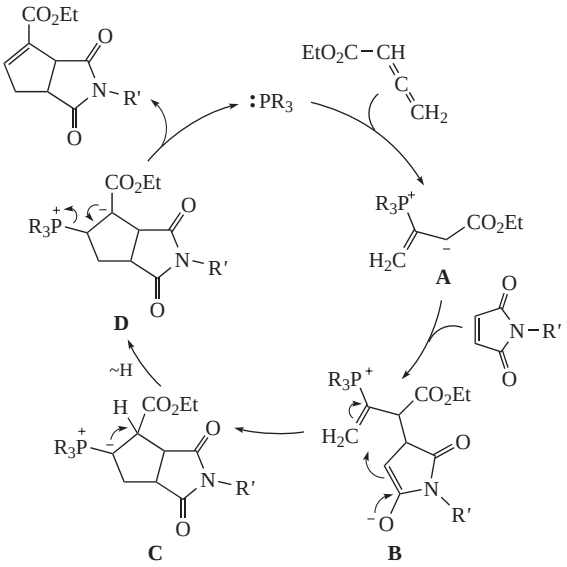
Ethyl 2-benzyl-1,3-dioxo-1,2,3,3a,6,6a-hexahydrocyclopenta[c]*pyrrole-4-carboxylate* **19**[26] was obtained from compound **10** (56 mg, 0.3 mmol) and allene **18** (67 mg, 0.6 mmol) in the presence of PPh_3 (8 mg, 10 mol%). Eluent: CH_2Cl_2–MeOH (250:1), yield 88 mg (98%), colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* 7.2 Hz), 2.85–3.03 (m, 2H), 3.53 (ddd, 1H, *J* 12.1, 8.3, 3.9 Hz), 4.17–4.21 (m, 1H), 4.27 (qd, 2H, *J* 7.2, 2.4 Hz), 4.61 (dd, 2H, *J* 16.8 Hz, 14.0 Hz), 6.76 (dd, 1H, *J* 4.4, 2.4 Hz), 7.25–7.35 (m, 5H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.2 (1C), 35.5 (1C), 42.5 (1C), 43.1 (1C), 51.6 (1C), 61.0 (1C), 127.9 (1C), 128.6 (2C), 128.7 (2C), 133.1 (1C), 135.5 (1C), 143.8 (1C), 163.1 (1C), 175.1 (1C), 178.5 (1C).

Ethyl 2-(4-methylphenyl)-1,3-dioxo-1,2,3,3a,6,6a-hexahydrocyclopenta[c]*pyrrole-4-carboxylate* **20** was obtained from compound **11** (56 mg, 0.3 mmol) and allene **18** (67 mg, 0.6 mmol) in the presence of PPh_3 (8 mg, 10 mol%). Eluent: CH_2Cl_2–MeOH (200:1), yield 87 mg (97%), white crystalline powder, mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, 3H, *J* 7.1 Hz), 2.36 (s, 3H), 3.03–3.07 (m, 2H), 3.67–3.72 (m, 1H), 4.22–4.35 (m, 3H), 6.86 (dd, 1H, *J* 4.5, 2.1 Hz), 7.13 (d, 2H, *J* 8.4 Hz), 7.25 (d, 2H, *J* 8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.1 (1C), 21.1 (1C), 35.9 (1C), 43.2 (1C), 51.6 (1C), 61.0 (1C), 126.2 (2C), 129.0 (1C), 129.7 (2C), 133.4 (1C), 138.6 (1C), 144.0 (1C), 163.1 (1C), 174.4 (1C), 178.1 (1C). HRMS (ESI), *m*/*z*: 322.10550 $[M+Na]^+$ (calc. for $C_{17}H_{17}NNaO_4$, *m*/*z*: 322.10553).

Ethyl 2-(1-adamantylmethyl)-1,3-dioxo-1,2,3,3a,6,6a-hexahydrocyclopenta[c]*pyrrole-4-carboxylate* **22** was obtained from compound **13** (74 mg, 0.3 mmol) and allene **18** (67 mg, 0.6 mmol) in the presence of PPh_3 (8 mg, 10 mol%). Eluent: CH_2Cl_2, yield 106 mg (99%), white crystalline powder, mp 89–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* 7.1 Hz), 1.44–1.45 (m, 6H), 1.55–1.67 (m, 6H), 1.92 (br.s, 3H), 2.92 (dq, 1H, *J* 19.6, 2.9 Hz), 3.00 (ddt, 1H, *J* 19.6, 10.0, 2.4 Hz), 3.18 (dd, 2H, *J* 16.3, 13.3 Hz), 3.54 (ddd, 1H, *J* 10.1, 8.2, 4.1 Hz), 4.17–4.21 (m, 1H), 4.28 (q, 2H, *J* 7.2 Hz), 6.79 (dd, 1H, *J* 4.4, 2.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.1 (1C), 28.1 (3C), 35.3 (1C), 35.7 (1C), 36.5 (3C), 40.6 (3C), 43.0 (1C), 50.0 (1C), 51.4 (1C), 60.8 (1C), 133.6 (1C), 143.4 (1C), 163.1 (1C), 176.0 (1C), 179.4 (1C). HRMS (ESI), *m*/*z*: 380.1832 $[M+Na]^+$ (calc. for $C_{21}H_{27}NNaO_4$, *m*/*z*: 380.1838).

Ethyl 2-(2-adamantylmethyl)-1,3-dioxo-1,2,3,3a,6,6a-hexahydrocyclopenta[c]*pyrrole-4-carboxylate* **25** was obtained from compound **16** (74 mg, 0.3 mmol) and allene **18** (67 mg, 0.6 mmol) in the presence of PPh_3 (8 mg, 10 mol%). Eluent: CH_2Cl_2, yield 102 mg (95%), white crystalline powder, mp 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, 3H, *J* 7.1 Hz), 1.48–2.02 (m, 15H), 2.87 (dq, 1H, *J* 19.7, 3.1 Hz), 2.97 (ddt, 1H, *J* 19.7, 10.4, 2.3 Hz), 3.48–3.62 (m, 3H), 4.14–4.18 (m, 1H), 4.26 (qd, 2H, *J* 7.1, 1.9 Hz), 6.74 (dd, 1H, *J* 4.4, 2.3 Hz). ^{13}C NMR (100.6 MHz, 353 K, DMSO-d_6) δ: 13.3 (1C), 26.9 (1C), 27.0 (1C), 29.1 (1C), 30.6 (2C), 34.6 (2C), 37.1 (1C), 37.9 (2C), 40.5 (1C), 41.5 (1C), 42.3 (1C), 51.1 (1C), 59.4 (1C), 132.5 (1C), 142.7 (1C), 162.2 (1C), 175.0 (1C), 178.2 (1C). HRMS (ESI), *m*/*z*: 380.1832 $[M+Na]^+$ (calc. for $C_{21}H_{27}NNaO_4$, *m*/*z*: 380.1838).

For characteristics of compounds **21**, **23**, **24** and **26**, see Online Supplementary Materials.



Scheme 3

lower yields for compounds **21** and **22** (26 and 51%, respectively). The mechanism of this cycloaddition process was described[2] and includes the following steps (Scheme 3). The nucleophilic addition of phosphine to an activated allene with the formation of a zwitter-ion structure **A** followed by the nucleophilic addition of this intermediate to the C=C bond of maleimide affords zwitter-ion **B**. The latter undergoes intramolecular cyclization giving **C**, the proton shift in this intermediate leads to precursor **D** which produces the final bicyclic molecule after elimination of phosphine. The liberated phosphine continues the catalytic cycle. The addition of phosphine to maleimide **1** is a side process causing oligomerization of the reactant thus diminishing the yield of the target product.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.003.

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