Synthesis A. I. Khatri, S. D. Samant Paper

Facile, Diversity-Oriented, Normal-Electron-Demand Diels–Alder Reactions of 6-Amino-2*H*-pyran-2-ones with Diethyl Acetylenedicarboxylate, 1,4-Naphthoquinone, and *N*-Phenylmaleimide

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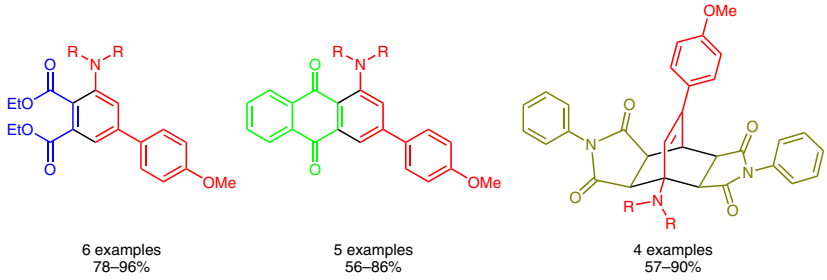

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Abstract A series of 6-amino-4-methoxyphenyl-2*H*-pyran-2-ones, having an electron-rich diene system, capable of undergoing normal-electron-demand (NED) Diels–Alder reaction, were synthesized. The Diels–Alder reaction of these pyrones with electron-deficient dienophiles – diethyl acetylene dicarboxylate, 1,4-naphthoquinone, and *N*-phenylmaleimide – followed three different pathways and gave structurally diverse products, aminobenzenes, aminoanthraquinones, and aminopolycyclic diimides, respectively. The amino group at the 6-position activated substantially the pyrone ring towards NED Diels–Alder reaction and the reaction has a potential to generate great structural diversity.

Key words 6-amino-2*H*-pyrone, normal-electron-demand Diels–Alder reaction, diversity-oriented synthesis, aminobiphenyls, anthraquinones, polycyclic diimides

2-Pyrones are six-membered heterocycles having weak aromatic character and hence exhibiting diene character in cycloadditions. Diels–Alder (DA) reaction of 2-pyrone is known. In fact, the first report of the DA reaction of 2-pyrones appeared in 1931.[1] The peculiarity of this reaction is that the reaction gives a bicyclic lactone product, which undergoes decarboxylation via a facile retro-DA reaction, to form a stable product. A variety of dienophiles have been employed in the reaction over the years.[2–9] The DA reactions of modified pyrones, like fused 2-pyrones,[10,11] and highly substituted 2-pyrones are reported.[12] The DA reactions of 3-hydroxy-2-pyrone requires a base as a catalyst,[13–15] longer reaction times or harsh conditions,[16] while the DA reactions of protected amino group at C3 position of pyrone lead to amino-substituted polycyclic compound.[7,12,17] Pyrones containing thio group like 3-phenylsulfenyl-2-pyrone[18] and 3-phenylsulfonyl-2-pyrone[19] react with electron-poor and electron-rich dienophiles to afford respective adducts without loss of CO_2. Surprisingly, the 3,5-halo derivatives of 2-pyrones show ambident diene behavior, that is, they undergo the reaction by normal-electron-demand (NED) as well as inverse-electron-demand (IED) pathways.[20,21] Intramolecular DA reaction on pyrones has a potential to generate complex systems.[22,23] The DA reaction of 2-pyrones has been employed in the synthesis of many natural products and related compounds,[24–26] like quinones,[14,15] benzenoids,[27,28] and complex bicyclo compounds.[29]

The diene behavior of 2-pyrones can be modified by introducing appropriate substituents on the ring. For the NED Diels–Alder reaction, an electron-rich diene is required, and hence an electron-donating group on the pyrone ring facilitates the reaction. Thus, the DA reactions of the pyrones bearing OMe and Me groups at the C6 position are reported. In spite of having electron-donating ability of OMe at C6 position, the DA reaction of 6-methoxypyrone requires long reaction time.[30,31]

In an effort to build polycyclic compounds bearing an amino group, which are difficult to synthesize otherwise, we thought of introducing an amino group at the 6-position of 2-pyrone through the DA reaction of the 2-pyrones and using this substrate as a diene. Surprisingly, the dienes containing an amino group at C6 position have not attracted attention. The amino group is not only expected to activate the diene, but also would provide amino group-substituted unusual products, which may be biologically interesting. While studying the NED Diels–Alder reaction of these 6-amino-2-pyrones with some symmetrical dienophiles we found that the reaction followed different pathways and gave structurally diverse products, exhibiting a diversity oriented synthesis (DOS). Thus, we are presenting our results on the facile, NED, diversity-oriented DA reaction of 6-amino-2-pyrones with diethyl acetylenedicarboxylate, 1,4-naphthoquinone (NQ), and *N*-phenylmaleimide (NPMA),

providing aminobenzenes, aminoanthraquinones, and aminopolycyclic diimides, respectively. Such compounds are useful, but difficult to obtain otherwise. For example, polysubstituted aromatic amines are useful in many fields like pharmaceuticals, dyes, and natural products.[32] Derivatives of phthalates are biologically active.[33–35] 3-Amino-substituted phthalic acid derivatives show IMP-1 metallo-β-lactamase inhibitory activity.[36] Aminoanthraquione is one of the core structures for drugs, dyes, etc.[37–42] 1-Amino-9,10-anthraquinones have anticancer properties.[43,44] The polycyclic diimides are one of the important building blocks in organic synthesis.[17] Moreover, bicyclo[2.2.2]octenes with amino group at the bridgehead are not common,[45] and their derivatives possess antiprotozoal activity.[46,47]

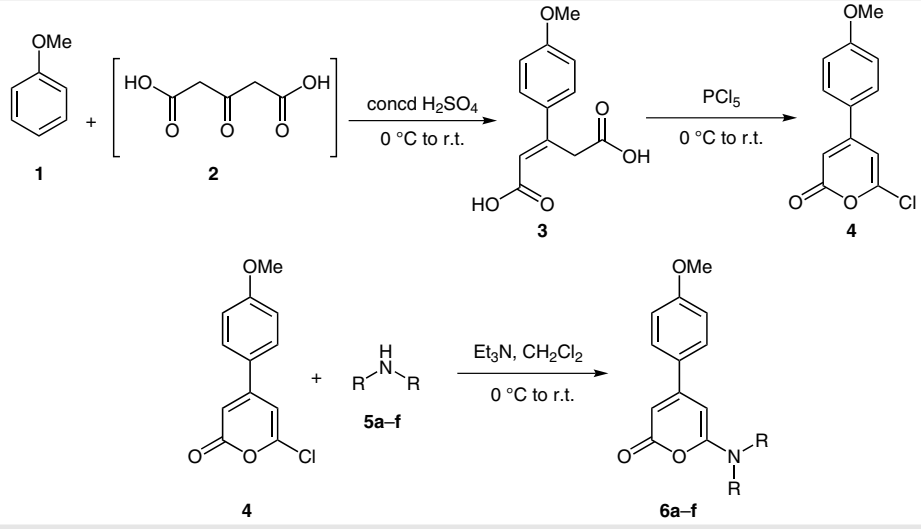
The 6-amino-2-pyrones **6** were synthesized as shown in Scheme 1. Acid **3** was synthesized by reacting anisole (**1**) with acetone dicarboxylic acid (**2**), prepared in situ from citric acid and concentrated sulfuric acid.[48] Acid **3** was treated with phosphorus pentachloride to obtain the corresponding 6-chloro derivative **4**,[21] which on reacting with dialkylamines **5** in the presence of triethylamine as a base gave the required 6-amino-2-pyrones **6** (Table 1).

Table 1 Synthesis of 6-Amino-2-pyrones **6**[a]

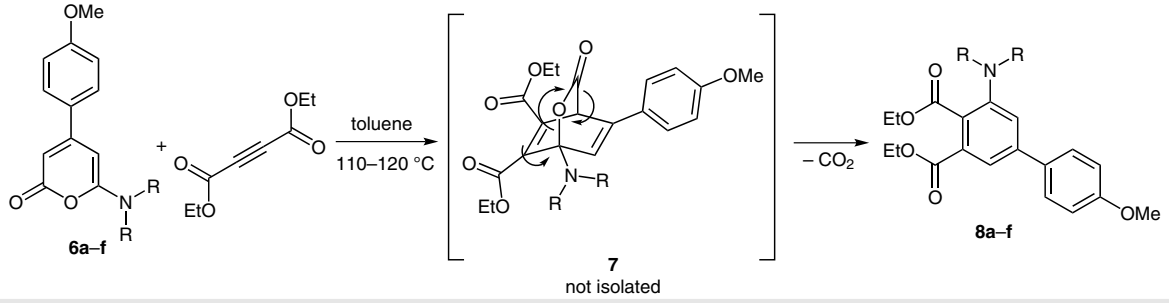
Entry	Amine **5**	2-Pyrone **6**	Yield (%)[b]
1	piperidine (**5a**)	**6a**	94
2	dimethylamine (**5b**)	**6b**	86
3	morpholine (**5c**)	**6c**	83
4	pyrollidine (**5d**)	**6d**	84
5	dibutylamine (**5e**)	**6e**	87
6	diethylamine (**5f**)	**6f**	81

[a] Reaction conditions: **4** (2 mmol), amine **5** (2.4 mmol), Et_3N (2 mmol), CH_2Cl_2 (12 mL), 0 °C to r.t., 3.5 h.
[b] Isolated yield.

The 6-amino-2-pyrones **6** were then used in Diels–Alder reactions with diethyl acetylenedicarboxylate in boiling toluene, leading to highly substituted benzeneamine derivatives **8a–f** (Scheme 2,Table 2). The normal-electron-demand Diels–Alder reaction first led to the formation of a bicyclic lactone **7**, which underwent decarboxylation to form the aromatized product **8**.



Scheme 1 Synthesis of 6-amino-2-pyrones **6**



Scheme 2 DA reaction of 6-amino-2-pyrones **6** with diethyl acetylenedicarboxylate

Table 2 Reaction of 6-Amino-2-pyrones **6** with Diethyl Acetylenedicarboxylate[a]

Entry	2-Pyrone **6**	Product **8**	Yield (%)[b]
1	**6a**	**8a**	78
2	**6b**	**8b**	92
3	**6c**	**8c**	96
4	**6d**	**8d**	85
5	**6e**	**8e**	79
6	**6f**	**8f**	95

[a] Reaction conditions: pyrone **6** (0.5 mmol), diethyl acetylenedicarboxylate (1 mmol), toluene (5 mL), reflux (110–120 °C), 2 h.
[b] Isolated yield.

Table 3 Reaction of 6-Amino-2-pyrones **6** with 1,4-Naphthoquinone[a]

Entry	2-Pyrone **6**	Product **11**	Yield (%)[b]
1	**6a**	**11a**	83
2	**6b**	**11b**	56
3	**6c**	**11c**	74
4	**6d**	**11d**	85
5	**6e**	**11e**	86

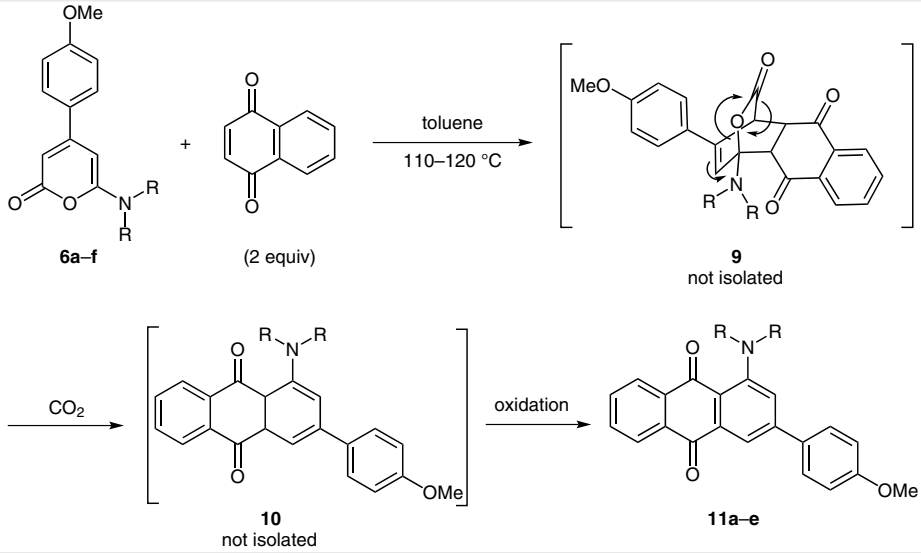
[a] Reaction conditions: pyrone **6** (0.5 mmol): 1,4-naphthoquinone (1 mmol), toluene (5 mL), reflux (110–120 °C), 3 h.
[b] Isolated yield.

The Diels–Alder reaction of **6** with 1,4-naphthoquinone in boiling toluene gave 1-amino-3-aryl- 9,10-anthraquinones **11a**–**e** (Scheme 3). This reaction took place in a different manner. The initial reaction gave a bicyclic lactone **9**, which underwent decarboxylation to form a dihydroanthraquinone derivative, which could not be isolated. 1,4-Naphthoquinone, being an oxidizing agent, probably oxidized the intermediate **10** to form the red colored 1-amino-3-(4-methoxyphenyl)-9,10-anthraquinones **11a**–**e** (Table 3). 1,4-Naphthoquinone is a known oxidant for the adducts in the Diels–Alder reaction.[14]

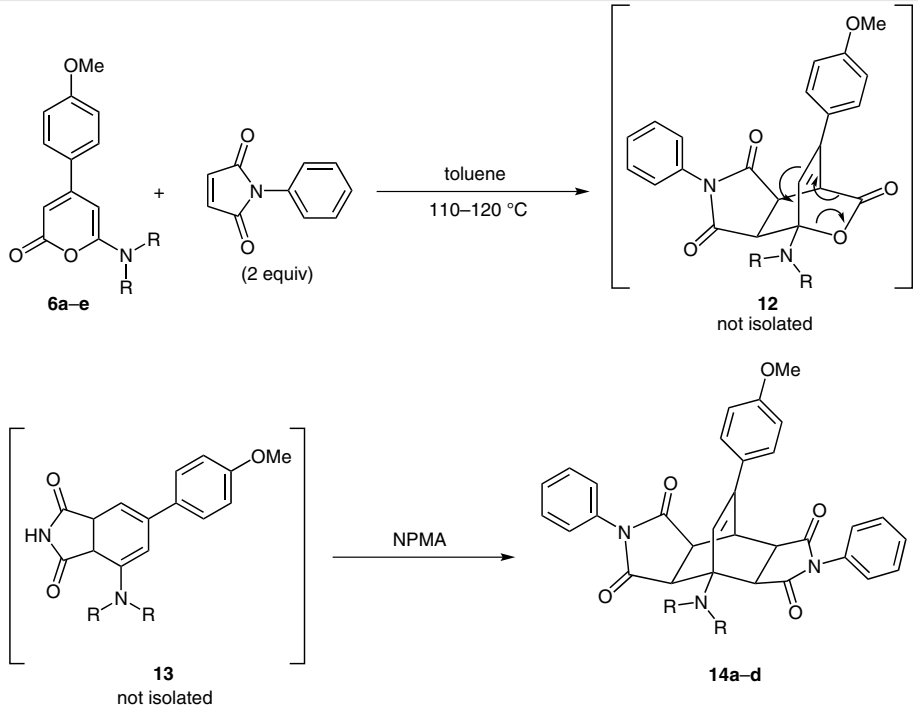
One of the most important synthetic routes for the synthesis of bicyclo[2.2.2]octenes is the Diels–Alder reaction of 2-pyrones.[17,49] The Diels–Alder reaction of **6** with *N*-phenylmaleimide gave polycyclic diimides **14a**–**d** (Table 4). The reaction took place via a tandem DA reaction–decarboxylation–DA reaction sequence. The intermediate **12** underwent decarboxylation to form a very reactive diene **13**, which reacted further with *N*-phenylmaleimide to form the adduct **14** (Scheme 4). Thermal Diels–Alder reactions of 2-pyrone gives *exo*,*exo*-fused ring products with a plane of symmetry.[17,49]

Thus, the DA reaction of 6-amino-2-pyrones leads to amino-substituted products. The reaction can be used in the synthesis of more complex structures; however, the reaction of electronically neutral dienophiles, like phenylacetylene, failed to give the desired product.

In conclusion, we have found the synthetic utility of 6-amino-2-pyrones in the synthesis of diverse compounds with high complexity, which is otherwise difficult to synthesize. This is the first report of DA reaction of 2-pyrones with amino group at the C6 position. The amino group enhances the reactivity of the pyrone as a diene, much better than a methoxy group does, and the reaction proceeds under the mild thermal conditions, through the normal electron demand pathway. The amino group is incorporated in the final product. Thus, the reaction represents a diversity-oriented synthesis. The products obtained may be commercially important and may find many applications in diverse fields.



Scheme 3 DA Reaction of 6-amino-2-pyrones **6** with 1,4-naphthoquinone



Scheme 4 DA Reaction of 6-amino-2-pyrones **6** with NMPA

Table 4 Reaction of 6-Amino-2-pyrones **6** with NMPA[a]

Entry	2-Pyrone **6**	Product **14**	Yield (%)[b]
1	**6a**	**14a**	87
2	**6b**	**14b**	90
3	**6d**	**14c**	87
4	**6e**	**14d**	57

[a] Reaction conditions: pyrone **6** (0.5 mmol), NMPA (1 mmol), toluene (5 mL), reflux (110–120 °C), 2 h,
[b] Isolated yield.

Melting points were determined on a Analab apparatus (Model-µThermocal 10) in open capillary tubes and are uncorrected. NMR spectra were recorded on Varian Mercury plus 300 spectrometer at 300 MHz or Bruker Avance spectrometer at 400 MHz using TMS as an internal standard. The coupling constants (*J*) are given in hertz. IR spectra were recorded on a Perkin-Elmer Spectrum 100 spectrophotometer as KBr pellet/$CHCl_3$. The starting compound **3** was prepared according to the reported procedure.[48] All other reagents and solvents are of commercial grade and used as such. Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range.

6-Chloro-4-(4-methoxyphenyl)-2*H*-pyran-2-one (4)[50]

To an ice cold, magnetically stirred, solution of PCl_5 (17 g, 82 mmol) in CH_2Cl_2 (60 mL) was added **3** (10 g, 42 mmol) portionwise. Vigorous reaction occurred during the addition. After stirring for 15 min, the ice bath was removed and the reaction mixture was stirred further for 3.5 h. The mixture was quenched with crushed ice, the organic layer was separated and washed with brine (50 mL), dried (Na_2SO_4), and the solvent evaporated under reduced pressure. The crude product was purified on silica gel (60–120 mesh) column chromatography using EtOAc–PE with increasing quantity of EtOAc; yield: 6 g (60%); pale yellow solid; mp 110–112 °C (Lit.[50] mp 216–217 °C).

IR (KBr): 1717, 1597, 1251, 1025, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 6.36 (d, *J* = 1.2 Hz, 1 H), 6.54 (d, *J* = 1.2 Hz, 1 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 104.0, 106.1, 114.8, 126.7, 128.3, 149.5, 155.5, 161.3, 162.3.

6-Amino-2*H*-pyrones 6; General Procedure

Pyranone **4** (473 mg, 2 mmol) was added to a 100 mL round-bottomed flask containing CH_2Cl_2 (12 mL), and equipped with a magnetic stirring. The reaction mixture was cooled using an ice-water bath. To the above solution, amine **5** (2.4 mmol) was added slowly followed by the addition of Et_3N (200 mg, 2 mmol). Ice-bath was removed after 30 min and the reaction mixture was further stirred for 3.5 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using EtOAc–PE by gradually increasing the quantity of EtOAc to afford the pure product.

4-(4-Methoxyphenyl)-6-(piperidin-1-yl)-2*H*-pyran-2-one (6a)

Yield: 536 mg (94%); yellow solid; mp 156–158 °C.

IR (KBr): 2939, 1738, 1569, 1366, 1228, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (6 H), 3.5 (4 H), 3.85 (s, 3 H), 5.64 (s, 1 H), 5.42 (s, 1 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.52 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.2, 45.9, 55.4, 80.8, 92.6, 114.2, 128.1, 130.3, 159.4, 161.2, 161.3, 162.5.

MS (ESI): m/z = 286 $[M + H]^+$.

ESI-MS: m/z calcd for $C_{17}H_{20}NO_3$ + H $[M^+ + H]$: 286.1443; found: 286.1430.

4-(4-Methoxyphenyl)-6-dimethylamino-2*H*-pyran-2-one (6b)

Yield: 422 mg (86%); yellow solid; mp 174–176 °C.

FTIR (KBr): 2928, 1709, 1607, 1242, 1023, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.16 (s, 6 H), 3.86 (s, 3 H), 5.31 (d, J = 1.2 Hz, 1 H), 5.65 (d, J = 1.2 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.54 (d, J = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9, 37.5, 55.4, 80.1, 92, 114.2, 128.1, 130.2, 159.3, 161.2, 162.0, 162.4.

MS (EI): m/z = 245 $[M]^+$.

ESI-MS: m/z calcd for $C_{14}H_{16}NO_3$ + H $[M^+ + H]$: 246.1130; found: 246.1128.

4-(4-Methoxyphenyl)-6-(morpholin-4-yl)-2*H*-pyran-2-one (6c)[51]

Yield: 477 mg (83%); yellow solid; mp 138–140 °C (Lit.[51] mp 148–149 °C).

FTIR (KBr): 2912, 1727, 1607, 1229, 1111, 798, 770 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.48 (t, J = 4.8 Hz, 4 H), 3.80 (t, J = 4.8 Hz, 3 H), 3.85 (s, 3 H), 5.42 (d, J = 1.5 Hz, 1 H), 5.76 (d, J = 1.5 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.52 (d, J = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.8, 55.4, 66, 81.1, 94.7, 114.3, 128.1, 129.8, 159, 161.4, 161.4, 162.0.

MS (EI): m/z = 287 $[M]^+$.

4-(4-Methoxyphenyl)-6-(pyrolidin-1-yl)-2*H*-pyran-2-one (6d)

Yield: 456 mg (84%); yellow solid, mp 162–164 °C.

IR (KBr): 2923, 1706, 1588, 1245, 1028, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.00–2.09 (m, 4 H), 3.48–3.52 (m, 4 H), 3.85 (s, 3 H), 5.22 (s, 1 H), 5.61 (s, 1 H), 6.68 (d, J = 8.7 Hz, 2 H), 7.54 (d, J = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.20, 46.71, 55.40, 91.27, 114.18, 128.08, 130.22, 159.15, 160.27, 161.18, 162.71.

MS (EI): m/z = 271 $[M]^+$.

ESI-MS: m/z calcd for $C_{16}H_{18}NO_3$ + H $[M^+ + H]$: 272.1287; found: 272.1281.

4-(4-Methoxyphenyl)-6-dibutylamino-2*H*-pyran-2-one (6e)

Yield: 573 mg (87%); yellow solid; mp 82–84 °C.

FTIR (KBr): 2958, 2923, 1720, 1526, 1248, 1023, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94–0.99 (m, 6 H), 1.25–1.39 (m, 4 H), 1.40–1.68 (m, 4 H), 3.37 (t, J = 7.5 Hz, 4 H), 3.85 (s, 3 H), 5.29 (s, 2 H), 5.6 (s, 1 H), 6.96 (d, J = 9 Hz, 2 H), 7.51 (d, J = 9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 20.2, 29.8, 48.6, 55.4, 80, 91.2, 114.2, 128.1, 130.5, 159.3, 161.1, 161.3, 162.6.

MS (EI): m/z = 329 $[M]^+$.

ESI-MS: m/z calcd for $C_{20}H_{28}NO_3$ + H $[M^+ + H]$: 330.2069; found: 330.2063.

4-(4-Methoxyphenyl)-6-diethylamino-2*H*-pyran-2-one (6f)

Yield: 443 mg (81%); yellow solid; mp 128–130 °C.

FTIR (KBr): 2978, 1708, 1605, 1176, 794 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 6 H), 3.47 (q, J = 7.2 Hz, 4 H), 3.86 (s, 3 H), 5.30 (s, 1 H), 5.61 (s, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 42.9, 55.4, 91.3, 114.2, 128.1, 130.5, 159.5, 161, 161.2, 162.6.

MS (EI): m/z = 273 $[M]^+$.

ESI-MS: m/z calcd for $C_{16}H_{20}NO_3$ + H $[M^+ + H]$: 274.1443; found: 274.1444.

Cycloaddition of 6-Amino-2-pyrones 6 with Diethyl Acetylenedicarboxylate; General Procedure

To a solution of 6-amino-2-pyrone 6 (0.5 mmol) in toluene (5 mL) was added diethyl acetylenedicarboxylate (170 mg, 1 mmol) and the reaction mixture was refluxed under N_2 atmosphere for 2 h. Toluene was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (60–120 mesh) using EtOAc–PE by gradually increasing the quantity of EtOAc to afford the pure product.

Diethyl 3-(Piperidin-1-yl)-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8a)

Yield: 156 mg (78%); white crystals; mp 83–85 °C.

FTIR (KBr): 2926, 1726, 1604, 1514 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.2 Hz, 3 H), 1.42 (t, J = 7.2 Hz, 3 H), 1.53–1.56 (m, 2 H), 1.64–1.69 (m, 4 H), 2.96 (m, 4 H), 3.86 (s, 3 H), 4.35 (q, J = 7.2 Hz, 2 H), 4.42 (q, J = 7.2 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.51–7.53 (m, 3 H), 7.90 (d, J = 1.2 Hz, 1 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.3, 24.2, 26.6, 24.2, 26.6, 54.2, 55.4, 61.3, 61.4, 114.3, 123.8, 124.1, 128.3, 129.1, 132.3, 142.5, 153.0, 159.7, 165.7, 168.8.

MS (EI): m/z = 413 $[M]^+$.

ESI-MS: m/z calcd for $C_{24}H_{30}NO_5$ + H $[M^+ + H]$: 412.2124; found: 412.2125.

Diethyl 3-Dimethylamino-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8b)

Yield: 170 mg (92%); white crystals; mp 92–94 °C.

FTIR (KBr): 2981, 1726, 1600, 1519 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.40 (m, 6 H), 2.81 (s, 6 H), 3.86 (s, 3 H), 4.35 (q, J = 7.2 Hz, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.79 (d, J = 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 45.1, 55.4, 61.4, 61.5, 114.3, 122.2, 122.4, 128.3, 128.9, 130.0, 132.4, 142.5, 152.5, 159.7, 166.1, 169.0.

MS (EI): m/z = 371 $[M]^+$.

ESI-MS: m/z calcd for $C_{21}H_{25}NO_5$ + Na $[M^+ + Na]$: 394.1630; found: 394.1616.

Diethyl 3-(Morpholin-4-yl)-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8c)

Yield: 198 mg (96%); white crystals; mp 116–118 °C.

FTIR (KBr): 2956, 1724, 1600, 1521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.43 (m, 6 H), 3.05 (m, 4 H), 3.80 (m, 4 H), 3.87 (s, 3 H), 4.40 (m, 4 H), 7.01 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.8 Hz, 2 H), 7.54 (d, J = 1.6 Hz, 1 H), 7.97 (d, J = 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.3, 53.5, 55.4, 61.4, 61.6, 67.4, 114.4, 124.0, 124.6, 128.3, 129.2, 131.9, 132.1, 142.8, 151.3, 159.9, 165.4, 168.7.

MS (EI): *m*/*z* = 413 [M]$^+$.

ESI-MS: *m*/*z* calcd for $C_{23}H_{28}NO_6$ + H [M$^+$ + H]: 414.1917; found: 414.1891.

Diethyl 3-(Pyrolidin-1-yl)-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8d)

Yield: 170 mg (85%); white crystals; mp 108–112 °C.

FTIR (KBr): 2974, 1722, 1602, 1516 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.38 (m, 6 H), 1.93–1.97 (m, 4 H), 3.35 (t, *J* = 6.4 Hz, 4 H), 3.85 (s, 3 H), 4.31–4.38 (m, 4 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 7.02 (d, *J* = 1.2 Hz, 1 H), 7.36 (d, *J* = 1.2 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.3, 25.8, 50.0, 55.4, 61.4, 61.6, 114.2, 116.2, 116.4, 117.9, 128.4, 131.8, 133.1, 142.3, 146.6, 159.6, 167.5, 170.1.

MS (EI): *m*/*z* = 397 [M]$^+$.

ESI-MS: *m*/*z* calcd for $C_{23}H_{28}NO_5$ + H [M$^+$ + H]: 398.1967; found: 398.1968.

Diethyl 3-(Dibutylamino)-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8e)

Yield: 178 mg (79%); gum.

FTIR (KBr): 2980, 1726, 1600, 1514, 1178 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 6 H), 1.23–1.46 (m, 14 H), 2.98 (m, 4 H), 3.86 (s, 3 H), 4.33–4.42 (m, 4 H), 7.00 (d, *J* = 8.8 Hz, 2 H), 7.52 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 1.6 Hz, 1 H), 7.93 (d, *J* = 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1, 14.2, 20.4, 29.6, 54.8, 55.4, 61.2, 61.4, 114.4, 124.1, 126.1, 128.3, 129.2, 132.30, 133.1, 142.0, 151.0, 159.7, 165.7, 168.9.

MS (EI): *m*/*z* = 455 [M]$^+$.

ESI-MS: *m*/*z* calcd for $C_{27}H_{37}NO_5$ + H [M$^+$ + H]: 456.2750; found: 456.2749.

Diethyl 3-Diethylamino-5-(4-methoxyphenyl)benzene-1,2-dicarboxylate (8f)

Yield: 190 mg (95%); gum.

FTIR (KBr): 2980, 1726, 1602, 1715 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (m, 6 H), 1.4 (m, 6 H), 3.06 (m, 4 H), 3.89 (s, 3 H), 4.35–4.46 (m, 4 H), 7.02 (dd, *J* = 8.8, 2 Hz, 2 H), 7.99 (d, *J* = 2 Hz, 1 H), 7.57 (d, *J* = 2 Hz, 1 H), 7.55 (dd, *J* = 8.8, 2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 14.2, 14.2, 48.8, 55.4, 61.1, 61.5, 114.4, 124.5, 126.6, 128.3, 129.0, 132.2, 134.0, 142.1, 150.3, 159.8, 165.6, 168.8.

MS (EI): *m*/*z* = 399 [M]$^+$.

ESI-MS: *m*/*z* calcd for $C_{23}H_{30}NO_5$ + H [M$^+$ + H]: 400.2124; found: 400.2131.

Cycloaddition of 6-Amino-2-pyrones 6 with 1,4-Naphthoquinone; General Procedure

To a solution of 6-amino-2-pyrone **6** (0.5 mmol) in toluene (5 mL) was added 1,4-naphthoquinone (158 mg, 1 mmol). The reaction mixture was refluxed under N_2 atmosphere for 3 h. Toluene was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (60–120 mesh) using EtOAc–PE by gradually increasing the quantity of EtOAc to afford the pure product.

1-(Piperidin-1-y1)-3-(4-methoxyphenyl)-9,10-anthraquinone (11a)

Yield: 165 mg, 83%; dark red crystals; mp 186–188 °C.

FTIR (KBr): 2923, 1668, 1664, 1579, 1243, 1028, 827 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67–1.73 (m, 2 H), 1.84–194 (m, 4 H), 3.21–3.24 (t, *J* = 6.8 Hz, 4 H), 3.88 (s, 3 H), 7.22 (d, *J* = 12 Hz, 2 H), 7.55 (d, *J* = 2.4 Hz, 1 H), 7.66–7.79 (m, 4 H), 8.12 (d, *J* = 2.4 Hz, 1 H), 8.24 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 26.1, 54.2, 55.4, 114.5, 118.4, 120.7, 122.3, 126.4, 127.3, 128.5, 131.9, 132.5, 132.7, 134.1, 134.3, 135.7, 136.9, 146.1, 154.9, 160.3, 181.2, 184.6.

MS (ESI): *m*/*z* = 398.2 [M + H]$^+$.

ESI-MS: *m*/*z* calcd for $C_{26}H_{23}NO_3$ + H [M$^+$ + H]: 398.1756; found: 398.1755.

1-Dimethylamino-3-(4-methoxyphenyl)-9,10-anthraquinone (11b)

Yield: 100 mg (56%); red crystals; mp 176–178 °C.

FTIR (KBr): 2925, 1666, 1641, 1590, 1248, 1033, 812, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (s, 6 H), 3.88 (s, 3 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 7.46 (d, *J* = 1.6 Hz, 1 H), 7.66–7.91 (m, 4 H), 8.03 (d, *J* = 1.6 Hz, 1 H), 8.24–8.27 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3, 55.4, 114.4, 116.9, 118.3, 119.6, 126.5, 127, 128.5, 132.1, 132.6, 134.1, 136, 136.7, 145.7, 153.8, 160.3, 181.1, 184.5.

ESI-MS: *m*/*z* calcd for $C_{23}H_{19}NO_3$ + H [M$^+$ + H]: 358.1443; found: 358.1432.

3-(4-Methoxyphenyl)-1-(morpholin-4-yl)-9,10-anthraqunone (11c)

Yield: 148 mg (74%); red solid; mp 138–140 °C.

FTIR (KBr): 2922, 2860, 1663, 1583, 1250, 1025, 944, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.27–3.33 (m, 4 H), 3.89 (s, 3 H), 4.06–4.09 (m, 4 H), 7.03–7.07 (m, 2 H), 7.66–7.7 (m, 2 H), 7.56 (s, 1 H), 7.7–7.82 (m, 2 H), 8.22–8.31 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1, 55.5, 67.1, 114.5, 119.5, 121.2, 121.8, 126.5, 127.4, 128.5, 131.5, 132.4, 133, 134.2, 135.5, 137.0, 146.6, 154.0, 160.5, 181.4, 184.3.

ESI-MS: *m*/*z* calcd for $C_{25}H_{21}NO_4$ + H [M$^+$ + H]: 400.1549; found: 400.1541.

3-(4-Methoxyphenyl)-1-(pyrolidin-1-yl)-9,10-anthraquinone (11d)

Yield: 162 mg (85%); bright red solid; mp 196–198 °C.

FTIR (KBr): 2933, 1667, 1664, 1580, 1243, 1029, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (br, 4 H), 3.38 (br, 4 H), 3.87 (s, 3 H), 7.02 (dd, *J* = 9, 2.4 Hz, 2 H), 7.38 (s, 1 H), 7.99 (s, 1 H), 7.64–7.78 (m, 4 H), 8.12–8.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 31.0, 52.7, 55.4, 114.4, 115.5, 117.1, 117.5, 126.5, 126.6, 128.5, 132.3, 132.3, 132.7, 134, 136, 136.6, 145.2, 150.1, 160.1, 181.2, 184.5.

ESI-MS: *m*/*z* calcd for $C_{25}H_{21}NO_3$ + H [M⁺ + H]: 384.1600; found: 384.1592.

1-(Dibutylamino)-3-(4-methoxyphenyl)-9,10-anthraquinone (11e)

Yield: 190 mg (86%); dark pink crystals; mp 85–87 °C.

FTIR (KBr): 2952, 1631, 1660, 1588, 1245, 1029, 837, 715 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 6 H), 1.29 (m, 4 H), 1.84 (q, *J* = 7.2 Hz, 4 H), 3.62 (t, *J* = 7.2 Hz, 4 H), 3.89 (s, 3 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 2 H), 7.52 (d, *J* = 1.2 Hz, 1 H), 7.68–7.78 (m, 2 H), 8.03 (d, *J* = 1.2 Hz, 1 H), 8.26 (t, *J* = 8.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 20.3, 29.8, 52.8, 54.4, 114.5, 117.4, 120.2, 123.1, 126.4, 127.1, 128.4, 132.0, 132.5, 132.6, 134.0, 136, 136.9, 145.3, 153.1, 160.2, 180.6, 184.6.

ESI-MS: *m*/*z* calcd for $C_{29}H_{31}NO_3$ + H [M⁺ + H]: 442.2382; found: 442.2376.

Cycloaddition of 6-Amino-2-pyrones 6 with NMPA; General Procedure

To a solution of 6-amino-2-pyrone **6** (0.5 mmol) in toluene (5 mL) was added NPMA (173 mg, 1 mmol). The reaction mixture was refluxed under N_2 for 2 h. Toluene was evaporated under reduced pressure and the crude product was washed with cold Et_2O (2 × 4 mL) to afford the sufficiently pure product.

7-(Piperidin-1-y1)-13-(4-methoxyphenyl)-4,10-diphenyl-4,10-diazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradeca-13-ene-3,5,9,11-tetrone (14a)

Yield: 255 mg (87%); white solid; mp 264–266 °C (turned yellow).

FTIR (KBr): 2926, 1772, 1714, 1602, 1502, 1182 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (br, 4 H), 1.82 (br, 2 H), 3.24 (br, 4 H), 3.35 (dd, *J* = 8.4, 2.7 Hz, 2 H), 3.55 (d, *J* = 8.4 Hz, 2 H), 3.82 (s, 3 H), 4.38 (dt, *J* = 3, 1.5 Hz, 2H), 6.69 (s, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.02 (d, *J* = 6.6 Hz, 4 H), 7.27–7.45 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 26.2, 27.6, 36.4, 44.7, 45.5, 47, 47.6, 55.3, 67.8, 114.4, 121.6, 126.3, 127, 128.6, 129.1, 131.6, 140.4, 160.1, 173.9, 175.3.

MS (ESI): *m*/*z* = 588.2 [M]⁺.

ESI-MS: *m*/*z* calcd for $C_{36}H_{33}N_3O_5$ + H [M⁺ + H]: 588.2498; found: 588.2494.

13-(4-Methoxyphenyl)-7-(dimethylamino)-4,10-diphenyl-4,10-diazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradeca-13-ene-3,5,9,11-tetrone (14b)

Yield: 260 mg (90%); pale yellow solid; mp 253–254 °C (turned dark yellow).

FTIR (KBr): 1770, 1710, 1600, 1506, 1186 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.85–2.94 (br, 6 H), 3.34 (d, *J* = 8.4 Hz, 2 H), 3.36 (m, 2 H), 3.81 (s, 3 H), 4.39 (s, 1 H), 6.67 (s, 1 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 7.04 (d, *J* = 7.6 Hz, 4 H), 7.43–7.3 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3, 44.6, 44.9, 49.6, 55.3, 67.7, 114.43, 126.1, 126.2, 127.1, 128.6, 129.1, 129.2, 131.5, 134.2, 160.3, 174.0, 175.2.

ESI-MS: *m*/*z* calcd for $C_{33}H_{29}N_3O_5$ + H [M⁺ + H]: 548.2185; found: 548.2179.

13-(4-Methoxyphenyl)-7-(pyrolidin-1-yl)-4,10-diphenyl-4,10-diazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradeca-13-ene-3,5,9,11-tetrone (14c)

Yield: 250 mg (87%); white solid; mp 234–236 °C (turned yellow).

FTIR (KBr): 2962, 1770, 1714, 1600, 1188 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (br, 4 H), 3.30 (br, 4 H), 3.36 (dd, *J* = 8.4, 0.8 Hz, 2 H), 3.53 (d, *J* = 8.4 Hz, 2 H), 3.82 (s, 3 H), 4.08 (s, 1 H), 6.65 (s, 1 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 7.2 Hz, 4 H), 7.30–7.39 (m, 6 H), 7.43 (d, *J* = 8.4 Hz, 2 H).

ESI-MS: *m*/*z* calcd for $C_{35}H_{31}N_3O_5$ + H [M⁺ + H]: 574.2336; found: 574.2326.

13-(4-Methoxyphenyl)-7-(dibutylamino)-4,10-diphenyl-4,10-diazatetracyclo[5.5.2.0^{2,6}.0^{8,12}]tetradeca-13-ene-3,5,9,11-tetrone (14d)

Yield: 179 mg (57%); white solid; mp 238–240 °C (turned yellow).

FTIR (KBr): 2591, 1772, 1723, 1603, 1504, 1182 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 6 H), 0.88 (t, *J* = 7.2 Hz, 6 H), 1.22 (m, 2 H), 1.43 (m, 4 H), 1.79 (m, 2 H), 2.86 (t, *J* = 8 Hz, 2 H), 3.12 (t, *J* = 8 Hz, 2 H), 3.35 (d, *J* = 8.8 Hz, 2 H), 3.36 (d, *J* = 8.8 Hz, 2 H), 3.48 (d, *J* = 8.8 Hz, 2 H), 3.81 (s, 3 H), 4.38 (s, 1 H), 6.49 (s, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 4 H), 7.28–7.39 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.3, 20.1, 20.9, 32.19, 36.7, 36.9, 44.6, 45.5, 50.9, 52.7, 55.3, 68.8, 114.5, 122.8, 126.2, 127.1, 128.2, 128.6, 129.1, 131.6, 140.2, 160.1, 173.5, 175.3.

ESI-MS: *m*/*z* calcd for $C_{39}H_{41}N_3O_5$ + H [M⁺ + H]: 632.3124; found: 632.3100.

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References

(1) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1931**, *490*, 257.
(2) Ziegler, T.; Layh, M.; Effenberger, F. *Chem. Ber.* **1987**, *120*, 1347.
(3) Kranjc, K.; Kočevar, M. *Synlett* **2008**, 2613.
(4) Lee, J. J.; Kraus, G. A. *Tetrahedron Lett.* **2013**, *54*, 2366.
(5) Kamath, C. R.; Samant, S. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1999**, *38*, 1214.
(6) Karmarkar, K. S.; Samant, S. D. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1993**, *32*, 1113.
(7) Juranovič, A.; Kranjc, K.; Polanc, S.; Kočevar, M. *Synthesis* **2014**, *46*, 909.
(8) Kirkham, J. D.; Leach, A. G.; Row, E. C.; Harrity, J. *Synthesis* **2012**, *44*, 1964.
(9) Mander, L. N.; O'Sullivan, T. P. *Synlett* **2003**, 1367.
(10) Kranjc, K.; Polanc, S.; Kočevar, M. *Org. Lett.* **2003**, *5*, 2833.
(11) Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1984**, *49*, 4033.
(12) Kranjc, K.; Kočevar, M. *New J. Chem.* **2005**, *29*, 1027.
(13) Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1995**, *36*, 5939.
(14) Komiyama, T.; Takaguchi, Y.; Tsuboi, S. *Synlett* **2006**, 124.
(15) Komiyama, T.; Takaguchi, Y.; Tsuboi, S. *Synthesis* **2006**, 1405.

(16) Corey, E. J.; Kozikowski, A. P. *Tetrahedron* **1975**, *16*, 2389.
(17) Hren, J.; Polanc, S.; Kočevar, M. *ARKIVOC* **2008**, *(i)*, 209.
(18) Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083.
(19) Posner, G. H.; Nelson, T. D. *Tetrahedron Lett.* **1990**, *45*, 4573.
(20) Afarinkia, K.; Bearpark, M. J.; Ndibwami, A. *J. Org. Chem.* **2005**, *70*, 1122.
(21) Balázs, L.; Kádas, I.; Tõke, L. *Tetrahedron Lett.* **2000**, *41*, 7583.
(22) Shin, J.-T.; Shin, S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 5857.
(23) Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3339.
(24) Nelson, H. M.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 25.
(25) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-C. *J. Org. Chem.* **2008**, *73*, 6258.
(26) Zhao, P.; Beaudry, C. M. *Org. Lett.* **2013**, *15*, 402.
(27) Kohl, R. T.; Katto, T.; Braham, J. N.; Stille, J. K. *Macromolecules* **1978**, *11*, 340.
(28) Reed, A. J. Jr.; Schilling, C. L.; Tarvin, R. F.; Rettig, T. A.; Stille, J. K. *J. Org. Chem.* **1969**, *34*, 2188.
(29) Kranjc, K.; Perdih, F.; Kočevar, M. *J. Org. Chem.* **2009**, *74*, 6303.
(30) Jung, M. E.; Lowe, J. A. *J. Chem. Soc., Chem. Commun.* **1978**, 95.
(31) Jung, M. E.; Lowe, J. A. III; Lyster, M. A.; Node, M.; Pfluger, R. W.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751.
(32) Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, **2004**.
(33) Hiraiwa, Y.; Morinaka, A.; Fukushima, T.; Kudo, T. *Bioorg. Med. Chem. Lett.* **2013**, *21*, 5841.
(34) Moore, N. P. *Reprod. Toxicol.* **2000**, *14*, 183.
(35) Koch, H. M.; Drexler, H.; Angerer, J. *Int. J. Hyg. Envir. Heal.* **2003**, *206*, 77.
(36) Hiraiwa, Y.; Morinaka, A.; Fukushima, T.; Kudo, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5162.
(37) Christie, R. M. *Colour Chemistry*; Vol. 27; Royal Society of Chemistry: Cambridge, **2001**.
(38) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.
(39) Gaut, J. E.; Hodge, P.; Cupertino, D.; Helliwell, M. *New J. Chem.* **2006**, *30*, 1801.
(40) Kraska, J.; Blus, K. *Dyes Pigments* **1987**, *8*, 449.
(41) Peters, A. T. *J. Chem. Technol. Biotechnol.* **1991**, *51*, 171.
(42) Aguilar, D. A.; Aslam, M. Patent EP Appl. 0499451, **1992**; *Chem. Abstr.* **1992**, *117*, 251073.
(43) Mincher, D. J. Patent PCT Int. Appl. WO1995009149, **1995**; *Chem. Abstr.* **1995**, *123*, 112733.
(44) Kay, G.; Mincher, D.; Turnbull, A. Patent PCT Int. Appl. WO2001044190, **2001**; *Chem. Abstr.* **2001**, *135*, 46452.
(45) Kende, A. S.; Lan, J.; Arad, D. *Tetrahedron Lett.* **2002**, *43*, 5237.
(46) Berger, H.; Seebacher, W.; Kaiser, M.; Brun, R.; Saf, R.; Weis, R. *Monatsh. Chem.* **2009**, *140*, 495.
(47) Seebacher, W.; Brun, R.; Saf, R.; Kröpfl, D.; Weis, R. *Monatsh. Chem.* **2004**, *135*, 313.
(48) Sunder, S.; Peet, N. P. *Heterocycles* **1986**, *24*, 393.
(49) Kranjc, K.; Kočevar, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2001.
(50) Sule, D. V.; Karambelkar, N. P.; Deodhar, K. D.; Kulkarni, R. A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1980**, *19*, 648.
(51) Pednekar, S.; Jain, A. K.; Menon, K. K. *Indian J. Heterocycl. Chem.* **2004**, *14*, 1.