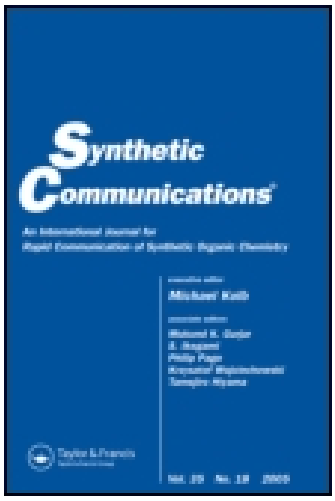

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A New and Improved *N*-3 Alkylation of 10-Substituted Isoalloxazines Using 1,8-Diazabicyclo[5.4.0]undec-7-ene in Benzene

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ABSTRACT

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been identified as a remarkable base for the alkylation at *N*-3 position of 10-substituted isoalloxazines with alkyl halides in dry benzene.

The flavin (isoalloxazine) cofactors FAD (flavin adenine dinucleotide) and FMN (flavin mononucleotide) are involved in a huge variety of biological transformations and electron transfer processes.[1–3] The diverse and vital process mediated by flavin cofactors has made structural analogs the focus of coenzyme inhibitor design and synthesis.[4]

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The isoalloxazine derivatives have been widely used in our research[5,6] and others[7,8] as synthetic models for flavoenzyme processes.

A wide variety of *N*-3 alkylisoalloxazines have been synthesized via a number of routes.[9–11] Some of these methods are restricted to methyl substitution,[9] slow reaction rate,[10] low yields[11] and use of excess alkylating agents. In this article, we report an alternative simple procedure for the *N*-3 alkylation of 10-substituted isoalloxazines using DBU as a base. Bicyclic amidine, DBU is a non-nucleophilic base and has been used in a variety of organic reactions including esterification, condensation, cyclization, alkylation of active methylene compounds, etc.[12] The application of DBU in the alkylation of cyclic amide nitrogens as present at *N*-3 position of isoalloxazines is not reported so far.

RESULTS AND DISCUSSION

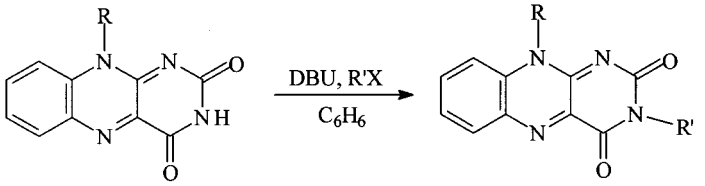
The reaction of 10-methylisoalloxazine with methyl iodide and DBU in dry benzene at room temperature for 1 h afforded 3,10-dimethylisoalloxazine in 97% yield (Table 1, Entry 1, Sch. 1). After the reaction, the DBU–hydroiodide (DBU–HI) complex was washed out with water from the reaction mixture. The product was purified by recrystallization (petroleum ether–benzene). The product was characterized by various spectroscopic data including UV–visible, IR, ^{1}H NMR, mass spectroscopy and elemental analysis. Similarly, the other isoalloxazines were also alkylated at *N*-3 position and characterized. The results of our synthetic study (Table 1) show that the reaction conditions afford high yields (87–97%) of the desired products. The required 10-substituted isoalloxazines were prepared according to the known literature procedure.[6,13]

N-3 Alkylation of isoalloxazines had been done by various methods[9–11] but the present procedure has some advantages over the conventional methods. First, a wide variety of *N*-3 alkylated isoalloxazines can be prepared under mild conditions. Secondly, the procedure is simple and easily scaled up. Thirdly, the reaction proceeds in non-polar solvent, making the work up very simple, products can be obtained in most of the cases in sufficiently pure form only by removal of DBU–HX. The process also avoids the use of excess alkyl halides.

The reaction of isoalloxazines with alkyl halides in the presence of usual base i.e., anhydrous K_2CO_3 is too slow to be used for the alkylation.[10] For example, the reaction of 10-butylisoalloxazine with hexadecylbromide and DBU in dry benzene at room temperature for 2.5 h afforded 3-hexadecyl-10-butylisoalloxazine in 90% yield (Entry 3),

Table 1. 3,10-Disubstituted isoalloxazines prepared.

Entry	*R*	*R′X*	Reaction time (h)	Yield (%)	M.p. (lit. m.p.)[Ref] (°C)
1	CH_3	CH_3I	1.0	97	304–305 (302–304)[14]
2	$(CH_2)_3CH_3$	CH_3I	1.0	95	307–308 (308)[15]
3	$(CH_2)_3CH_3$	$CH_3(CH_2)_{14}CH_2Br$	2.5	90	77–78 (77–80)[10]
4	$(CH_2)_5CH_3$	CH_3I	1.0	96	180 (180)[16]
5	$(CH_2)_5CH_3$	$CH_3(CH_2)_2CH_2Br$	1.5	94	153
6	$(CH_2)_5CH_3$	$CH_3(CH_2)_4CH_2Br$	1.5	90	106
7	$(CH_2)_5CH_3$	$CH_3(CH_2)_{10}CH_2Br$	2.0	89	98–99
8	$(CH_2)_5CH_3$	$CH_2{=}CH_2CH_2Br$	2.0	89	121
9	$(CH_2)_5CH_3$	$C_6H_5CH_2Br$	2.0	87	182
10	$(CH_2)_9CH_3$	CH_3I	1.0	92	156 (155)[16]
11	$(CH_2)_{11}CH_3$	CH_3I	1.0	94	177 (177–179)[16]
12	$(CH_2)_{15}CH_3$	CH_3I	1.0	96	140 (140)[16]
13	$(CH_2)_{15}CH_3$	$CH_3(CH_2)_2CH_2Br$	1.5	93	130
14	$(CH_2)_{15}CH_3$	$CH_3(CH_2)_4CH_2Br$	1.5	93	111
15	$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{10}CH_2Br$	2.0	89	104
16	$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{14}CH_2Br$	2.5	88	95
17	$(CH_2)_{17}CH_3$	CH_3I	1.0	91	157 (156–157)[16]
18	C_6H_5	CH_3I	1.0	93	>300 (>300)[9]
19	C_6H_5	CH_3CH_2Br	1.5	90	>300
20	2′-$CH_3C_6H_4$	CH_3I	1.0	90	>330 (>360)[17]
21	2′,6′-$CH_3C_6H_3$	CH_3I	1.0	89	295 (297–299)[14]
22	4′-ClC_6H_4	CH_3I	1.0	91	>300 (>300)[9]
23	4′-$OCH_3C_6H_4$	CH_3I	1.0	93	>330 (353–355)[17]
24	$C_6H_5CH_2$	CH_3I	1.0	89	282 (284)[9]



Scheme 1.

whereas the same reaction in the presence of anhydrous potassium carbonate under similar condition gave no product. The above reaction in anhydrous K_2CO_3/DMF gave 61% yield after two days.[10] High temperature (~100°C) and the long reaction time are usually required for the

synthesis of *N*-3 alkylisoalloxazines by means of alkyl halides and anhydrous K_2CO_3. Special care has to taken with methyl iodide i.e., moderate temperature with continuous circulation of cold water as methyl iodide is low boiling, whereas these conditions can be avoided using DBU as base.

In conclusion, our conditions for the *N*-3 alkylation of isoalloxazines are among the mildest available. DBU can be used as a base for alkylation of various *N*-10 alkyl/aryl-isoalloxazines and the reaction proceeds smoothly in a non-polar solvent at room temperature. Hence, the above procedure for the *N*-3 alkylation of isoalloxazines is superior to those methods as mentioned earlier.

EXPERIMENTAL

DBU and alkyl halides were obtained from Fluka, Switzerland and were used as such. All melting points were determined on Thomas Hoover Unimelt Capillary Apparatus and are uncorrected. IR spectra were recorded on Shimadzu TR-435 spectrometer (ν_{max} in cm^{-1}). Absorption spectra were recoreded on Shimadzu UV-260 spectrophotometer and absorption maxima were expressed in nm. ^{1}H NMR was recorded on Bruker Avance-300 spectrometer using TMS as an internal reference (chemical shift in ppm).

General Procedure for the *N*-3 Alkylation of 10-Substituted Isoalloxazines

DBU (0.5 mmol) was added to a solution of alkyl halide (0.6 mmol) and isoalloxazine (0.5 mmol) in dry benzene (50 mL). The reaction mixture was stirred at room temperature for the period given in Table 1 and washed with water. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residue was further washed with petroleum ether to remove the alkylating agent, if present and recrystallized from petroleum ether–benzene. In a few cases where starting materials was present, the residue was chromatographed over silica gel (60–120 mesh) using chloroform as an eluent.

3-Butyl-10-hexylisoalloxazine (5): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (29.27), 333 (6.92), 417 (6.32), 443 (7.56), 465 (5.17); ^{1}H NMR ($CDCl_3$): 8.27 (dd, 1H, 6-H, $J = 1.8$ and 8.2 Hz), 7.91 (t, 1H, 7-H), 7.59 (t, 1H, 8-H), 6.90 (d, 1H, 9-H, $J = 8.1$ Hz), 4.41 (t, 2H, N^{10}–CH_2), 3.55 (t, 2H, N^3–CH_2), 1.60–1.23 (m, 12H, $6 \times CH_2$), 0.90 (t,

6H, $2 \times CH_3$); IR (KBr): 2925, 2856, 2362, 1708, 1658, 1612, 1587, 1552, 1515, 1461, 1363, 1278, 1185, 806, 767, 720; MS *m*/*z* (% base): 354 (M^+, 97), 324 (10), 298 (16), 283 (85), 269 (49), 227 (72), 214 (100), 197 (20), 171 (37), 170 (71), 143 (30), 55 (29) and 43 (94); Anal. calcd. for $C_{20}H_{26}N_4O_2$: C, 67.77; H, 7.39; N, 15.81. Found: C, 67.72; H, 7.35; N, 15.78.

3,10-Dihexylisoalloxazine (6): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 266 (12.31), 333 (4.27), 422 (2.81), 443 (4.42), 472 (3.33); ^{1}H NMR ($CDCl_3$): 8.32 (dd, 1H, 6-H, $J = 1.6$ and 8.6 Hz), 7.90 (t, 1H, 7-H), 7.64–7.59 (m, 2H, 8-H and 9-H), 4.68 (t, 2H, N^{10}–CH_2), 3.50 (t, 2H, N^3–CH_2), 1.36–1.25 (m, 16H, $8 \times CH_2$), 0.93–0.86 (m, 6H, $2 \times CH_3$); IR (KBr): 2927, 2858, 2362, 1707, 1650, 1604, 1590, 1502, 1459, 1350, 1283, 1101, 1021, 970, 841, 775; MS *m*/*z* (% base): 382 (M^+, 29), 381 (69), 311 (57), 227 (60), 214 (100), 197 (17), 170 (58), 145 (27) and 43 (100); Anal calcd. for $C_{22}H_{30}N_4O_2$: C, 69.08; H, 7.90; N, 14.65. Found: C, 69.10; H, 7.88; N, 14.69.

3-Dodecyl-10-hexylisoalloxazine (7): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (42.05), 333 (10.14), 422 (7.67), 443 (10.72), 469 (6.90); ^{1}H NMR ($CDCl_3$): 8.17 (d, 1H, 6-H, $J = 8.13$ Hz), 7.99–7.96 (m, 2H, 7-H, 9-H), 7.66 (t, 1H, 8-H, $J = 7.73$ Hz), 4.60 (t, 2H, N^{10}–CH_2), 3.88 (t, 2H, N^3–CH_2), 1.74–1.24 (m, 28H, $14 \times CH_2$), 0.85 (t, 6H, $2 \times CH_3$); IR (KBr): 2921, 2851, 2362, 1712, 1654, 1558, 1519, 1462, 1347, 1281, 1183, 767; MS *m*/*z* (% base): 466 (M^+, 97), 423 (7), 396 (43), 339 (16), 299 (8), 227 (85), 214 (100), 170 (39), 143 (8) and 43 (100); Anal calcd. for $C_{28}H_{42}N_4O_2$: C, 72.07; H, 9.07; N, 12.01. Found: C, 72.12; H, 9.06; N, 12.03.

3-Allyl-10-hexylisoalloxazine (8): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 268 (94.25), 272 (94.25), 333 (20.84), 420 (21.73), 442 (26.82), 470 (18.10); ^{1}H NMR ($CDCl_3$): 8.32 (dd, 1H, 6-H, $J = 1.7$ and 8.6 Hz), 7.90 (t, 1H, 7-H, $J = 8.4$ Hz), 7.42 (t, 1H, 8-H, $J = 8.4$ Hz), 7.18 (dd, 1H, 9-H, $J = 1.2$ and 8.4 Hz), 5.39–5.13 (m, 3H, $CH{=}CH_2$), 4.74–4.72 (m, 2H, N^{10}–CH_2), 3.68 (d, 2H, N^3–CH_2), 1.34–1.25 (m, 8H, $4 \times CH_2$), 0.91 (t, 3H, CH_3); IR (KBr): 2926, 2855, 1718, 1648, 1611, 1588, 1558, 1513, 1459, 1339, 1281, 1197, 920, 769; MS *m*/*z* (% base): 338 (M^+, 15), 337 (70), 267 (78), 253 (92), 224 (17), 170 (64), 145, (81), 143 (29), 126 (68), 77 (18), 43 (78) and 41 (100); Anal calcd. for $C_{19}H_{22}N_4O_2$: C, 67.44; H, 6.55; N, 16.56. Found: C, 67.41; H, 6.48; N, 16.59.

3-Benzyl-10-hexylisoalloxazine (9): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (34.58), 334 (8.55), 423 (6.92), 443 (9.99), 472 (6.35); ^{1}H NMR ($CDCl_3$): 8.30 (dd, 1H, 6-H, $J = 1.6$ and 8.43 Hz), 7.86 (t, 1H, 7-H, $J = 7.3$ Hz), 7.63–7.58 (m, 3H, 8-H, 1′-H, 5′-H), 7.29–7.24 (m, 4H, 9-H, 2′, 3′, 4′-H), 5.30 (s, 2H, N^3–CH_2), 4.66 (t, 2H, N^{10}–CH_2), 1.39–1.28 (m,

8H, 4 × CH_2), 0.90 (t, 3H, CH_3); IR (KBr): 2925, 2855, 2362, 1710, 1659, 1588, 1557, 1460, 1281, 1183, 763, 708; MS *m*/*z* (% base): 388 (M^+, 14), 387 (52), 318 (26), 303 (42), 255 (25), 170 (31), 143 (17), 106 (54), 77 (16), 44 (100) and 43 (68); Anal calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.15; H, 6.20, N, 14.46.

3-Butyl-10-hexadecylisoalloxazine (13): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 265 (17.79), 334 (5.73), 420 (3.13), 442 (3.87), 466 (2.65); ^{1}H NMR ($CDCl_3$): 8.60 (dd, 1H, 6-H, $J = 1.8$ and 8.2 Hz), 7.90 (t, 1H, 7-H), 7.57 (t, 1H, 8-H), 6.93 (d, 1H, 9-H, $J = 8.1$ Hz), 4.65 (t, 2H, N^{10}–CH_2), 4.02 (t, 2H, N^3–CH_2), 1.60–1.23 (m, 32H, 16 × CH_2), 0.97 (t, 6H, 2 × CH_3); IR (KBr): 2926, 2854, 2362, 1712, 1682, 1610, 1589, 1554, 1514, 1458, 1280, 1192, 1115, 1070, 806, 767; MS *m*/*z* (% base): 494 (M^+, 25), 493 (71), 464 (21), 438 (51), 311 (41), 227 (52), 215 (22), 214 (59), 170 (9), 143 (21) and 43 (100); Anal calcd. for $C_{30}H_{46}N_4O_2$: C, 72.84; H, 9.37; N, 11.33. Found: C, 72.88; H, 9.34; N, 11.38.

3-Hexyl-10-hexadecylisoalloxazine (14): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (29.90), 334 (7.19), 421 (5.79), 443 (7.66), 469 (4.50); ^{1}H NMR ($CDCl_3$): 8.49 (dd, 1H, 6-H, $J = 1.6$ and 8.1 Hz), 7.88 (t, 1H, 7-H), 7.47 (t, 1H, 8-H), 6.98 (d, 1H, 9-H, $J = 8.2$ Hz), 4.63 (t, 2H, N^{10}–CH_2), 3.95 (t, 2H, N^3–CH_2), 1.66–1.24 (m, 36H, 18 × CH_2), 0.97 (t, 6H, 2 × CH_3); IR (KBr): 2921, 2850, 1712, 1655, 1613, 1590, 1558, 1520, 1492, 1463, 1374, 1283, 1185, 1116, 868, 766, 708; MS *m*/*z* (% base): 522 (M^+, 24), 521 (78), 311 (49), 297 (29), 227 (41), 214 (79), 170 (48), 143 (17) and 43 (100); Anal calcd. for $C_{32}H_{50}N_4O_2$: C, 73.52, H, 9.64; N, 10.72. Found: C, 73.57; H, 9.60; N, 10.73.

3-Dodecyl-10-hexadecylisoalloxazine (15): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (33.63), 334 (8.79), 423 (7.98), 443 (8.88), 472 (7.18); ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 8.32 (dd, 1H, 6-H, $J = 1.7$ and 8.2 Hz), 7.87 (t, 1H, 7-H), 7.37 (t, 1H, 8-H), 6.92 (d, 1H, 9-H, $J = 8.1$ Hz), 4.44 (t, 2H, N^{10}–CH_2), 3.88 (t, 2H, N^3–CH_2), 1.66–1.26 (m, 48H, 24 × CH_2), 0.98 (t, 6H, 2 × CH_3); IR (KBr): 2921, 2850, 1712, 1655, 1613, 1590, 1558, 1520, 1463, 1374, 1283, 1185, 920, 766; MS *m*/*z* (% base): 606 (M^+, 21), 604 (41), 388 (74), 317 (33), 303 (37), 274 (19), 214 (68), 170 (37), 143 (16), 91 (43), 44 (100) and 43 (92); Anal calcd. for $C_{38}H_{62}N_4O_2$: C, 75.20; H, 10.30; N, 9.23. Found: C, 75.24; H, 10.31; N, 9.28.

3,10-Dihexadecylisoalloxazine (16): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 272 (25.53), 334 (6.27), 424 (5.58), 444 (7.44), 468 (5.26); ^{1}H NMR ($CDCl_3$): 8.35 (dd, 1H, 6-H, $J = 1.6$ and 8.2 Hz), 7.83 (t, 1H, 7-H), 7.34 (t, 1H, 8-H), 6.82 (d, 1H, 9-H, $J = 8.1$ Hz), 4.43 (t, 2H, N^{10}–CH_2), 3.98 (t, 2H, N^3–CH_2), 1.68–1.25 (m, 56H, 28 × CH_2), 0.98 (t, 6H, 2 × CH_3); IR (KBr): 2926, 2854, 2362, 1712, 1682, 1610, 1589, 1554, 1514, 1458, 1280, 1192, 1115, 1070, 806, 767; MS *m*/*z* (% base): 662 (M^+, 21),

494 (86), 439 (9), 270 (10), 227 (75), 215 (37), 214 (54), 170 (11), 144 (7), 143 (57) and 43 (100); Anal calcd. for $C_{42}H_{70}N_4O_2$: C, 76.08; H, 10.64; N, 8.45. Found: C, 76.04; H, 10.69; N, 8.42.

3-Ethyl-10-phenylisoalloxazine (19): UV–visible ($CHCl_3$), λ_{max} (ε_{max}, mM): 273 (27.29), 337 (7.46), 425 (6.20), 445 (7.98), 469 (5.22); ^{1}H NMR ($CDCl_3$): 8.22 (d, 1H, 6-H, $J = 7.8$ Hz), 7.77–7.42 (m, 7H, 7-H, 8-H and Ar–H), 6.81 (d, 1H, 9-H, $J = 8.39$ Hz), 3.94 (q, 2H, N^3–CH_2), 1.17 (t, 3H, CH_3); IR (KBr): 2927, 2368, 1703, 1650, 1556, 1460, 1350, 1267, 1202, 766, 700; MS *m*/*z* (% base): 318 (M^+, 21), 303 (10), 289 (41), 241 (56), 227 (8), 170 (56), 77 (100) and 43 (48); Anal calcd. for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60. Found: C, 67.92; H, 4.40; N, 17.67.

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