Exploration of the Mitsunobu Reaction with Tosyl- and Boc-Hydrazones as Nucleophilic Agents

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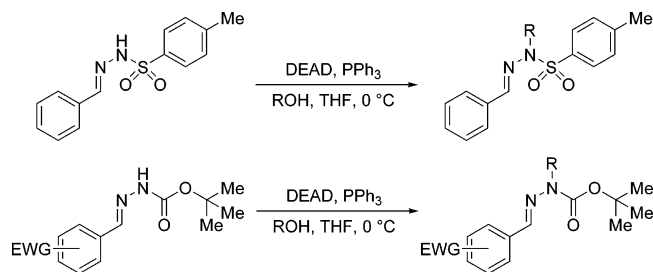
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Exploration of the Mitsunobu Reaction with Tosyl- and Boc-Hydrazones as Nucleophilic Agents

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FIGURE 1. Utility of functionalized hydrazones.

Tosyl- and Boc-hydrazones were found to be effective nucleophiles in the Mitsunobu reaction. Tosyl hydrazones reacted cleanly with primary and secondary alcohols when co-administered to a cooled DBAD/PPh$_3$ or DEAD/PPh$_3$ complex. Boc-hydrazones required electron-withdrawing substituents to participate in the reaction.

Hydrazones represent a versatile class of chemical intermediates capable of acting as both electrophiles[1] and nucleophiles.[2] Their ease of preparation, increased hydrolytic stability relative to imines, and tendency toward crystallinity are all desirable characteristics of hydrazones. Despite these positive traits, hydrazones have been under studied and much of their basic chemistry unexplored. Our interest in hydrazones was as nucleophilic partners in the Mitsunobu reaction. There are some examples in the literature of intramolecular Mitsunobu reactions with acyl hydrazones,[3] but we wished to extend the reaction to include tosyl- and Boc-hydrazones for intermolecular substitutions to give products of type 1 (Figure 1). Products of type 1 can in turn be converted into other useful products.[4]

We began our studies using the tosyl hydrazone of benzaldehyde (2) as our substrate as there is precedent for alkylation of tosyl hydrazones[5] and because sulfonamides are effective nucleophiles for the Mitsunobu reaction.[6] Indeed, when a THF solution of 2, benzyl alcohol, and Ph$_3$P were treated with di-*tert*-butyl azodicarboxylate (DBAD) at 0 °C (Method A),[7] the desired N-benzylated product was formed in good yield (Table 1, 4). These conditions were inefficient for secondary alcohols, however, giving poor conversions and an interesting tetrazan[8] side product (3, Figure 2) resulting from Michael-type addition of the hydrazone onto DBAD yielding a compound with four contiguous nitrogens.[9] Product 3 was isolable and chromatographable, but decomposed vigorously at its melting point (154 °C). Products such as 3 likely arise when the phosphonium-alcoxide electrophile reacts sluggishly, thus allowing the highly electrophilic DBAD to compete for the hydrazone nucleophile.

Formation of 3 could be prevented by premixing DBAD and PPh$_3$ at 0 °C for 10 min, which results in precipitation of the DBAD/PPh$_3$ adduct,[10] and then treating the heterogeneous mixture dropwise with a solution of alcohol and hydrazone (Method B). Method B substantially improved the yield when 2-indanol was the substrate (14B), but gave similar results as Method A with N-Boc-4-piperidinol (16B). Methods A and B were then reexamined by using diethyl azodicarboxylate (DEAD) instead of DBAD to give Methods C and D. Of the two, Method D gave higher yields, suggesting the steric environment surrounding the azodicarboxylate/ triphenylphosphine adduct plays a large role in reaction progression, and no products of type 3.[11] We then compared the effect of sequential addition of hydrazone and alcohol with co-addition. Treating the preformed DEAD/PPh$_3$ adduct sequentially with a solution of hydrazone followed by a solution of alcohol (Method E) gave nearly

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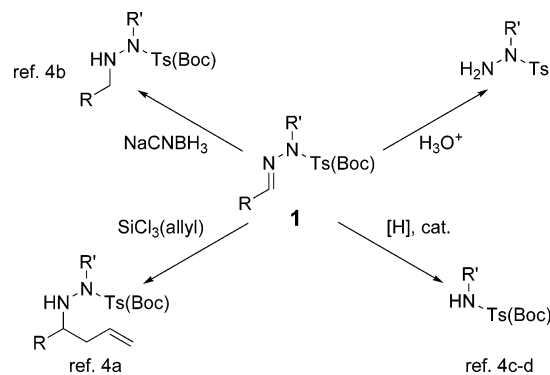(5) (a) Islam, A. M.; Abdel-Halim, A. M.; Salama, M. A. *Egypt. J. Chem.* 1987, 29, 405−431. (b) Donia, S. G.; Shams, N.; El-Rahman, T. A. *Ind. J. Chem., Sect. B* 1988, 27B, 117−120.

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(9) For entry 14 A, Table 1, a 24% yield of this side product was obtained.

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(11) We detected the DEAD derived tetrazan using Method C, but did not attempt to isolate this side product.

TABLE 1. Mitsunobu Reaction of 2 with Primary and Secondary Alcohols

Compound	Alcohol ROH	Method	Reaction time (hours)[a]	Yield (%)[b]
4	benzyl alcohol	A	2	88
		D	3	90
5	cyclopropylmethanol	D	1	96
6	TMS propargyl	D	1	95
7	BocN morpholine CH₂OH	D	4	91
8	sugar derivative	D	1.5	90
9	pyridyl CH₂OH	D	1.5	87
10	bromothiazolyl CH₂OH	B	2	96
		D	2	97
11	dibromoimidazolyl CH₂OH	D	1	90[c]
12	isopropanol	D	3	87
13	cyclopentanol	D	2	94
14	indanol	A	18	46
		B	3	77
		D	3	80
15	Boc dihydropyridinol	D	2	90
16	BocN piperidinol	A	2	40
		B	4	42
		C	18	35
		D	18	56
		E	4	58
		F	4	64

[a] Reactions typically failed to progress beyond 4 h. [b] Reactions were run with 100 mg of hydrazone; all yields are post silica gel column chromatography. [c] Alcohol was the limiting reagent.

identical results as co-addition Method D. Reversing the addition of alcohol and hydrazone (Method F) gave a slight improvement in yield (Table 1, **16**, Methods **D–F**). While there is a slight upward trend in yields for **16** with Methods **D–F**, the differences are too small to draw any mechanistic conclusions. Further clouding the mechanistic issue is that the reactions typically fail to progress beyond 4 h.[12] Further reaction optimization with phosphines[13] other than PPh₃ failed to give product when used in conjunction with Method D.
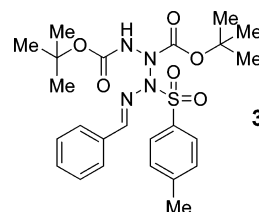
FIGURE 2. Tetrazan side product.

With the optimization studies complete, we examined a variety of primary and secondary alcohols, including allylic, benzylic, propargyllic, heterobenzylic, and simple alkanols (Table 1). For ease of TLC monitoring, the hydrazone was used as the limiting reagent for most of the examples. However, in those instances where the alcohol is precious, as with the alcohol precursor to **11**, the hydrazone can be used in excess and good yields obtained. Simple, highly reactive alcohols undergo clean conversion to the alkylated hydrazone with Method A or B, but as these methods did not appear to be as effective for secondary alcohols, we elected to use Method D for all substrates.

Boc-hydrazones[14] were then tested for effectiveness as nucleophiles in the Mitsunobu reaction with Method D. The Boc-hydrazone of benzaldehyde proved to be completely unreactive under all conditions examined, giving only recovered hydrazone. We were curious if the lack of observed reactivity was due to electronic[15] or steric factors. We prepared four increasingly electron poor and sterically crowded Boc-hydrazones and examined them in the Mitsunobu reaction with benzyl alcohol. We observed a gradual increase in reactivity as electron deficiency and steric-hindrance increased, suggesting pK_a of the hydrazone, and not steric bulk associated with the Boc group, was determining reactivity (Table 2). Indeed, the 2,6-dintrobenzaldehyde derivative gave a quite useful yield of substitution product (**20**).

In conclusion, we have extended the utility of the Mitsunobu reaction to include tosyl- and Boc-hydrazones as nucleophillic components. Preformation of a DEAD/PPh₃ complex prior to addition of alcohol and hydrazone (Method D) gave superior results than traditional methods (Method A or C) for secondary alcohols. Boc-hydrazones were found to be unreactive unless they possesed pK_a lowering substituents.

Experimental Section

Procedure A: To a round-bottomed flask are added the hydrazone substrate, alcohol (1.2 equiv), triphenylphosphine (1.4 equiv), and THF (0.2 M). The mixture is cooled to 0 °C (ice bath) and treated with DBAD (1.2 equiv) to give a bright yellow solution. The reaction is monitored by TLC until complete or no longer

(12) It remains unclear why this is the case though we have experienced this phenomenon with other systems as well, e.g. aryl/alkyl ether formation. Reactions were run under anhydrous conditions and with an inert atmosphere (N₂).

(13) Other phosphines examined: PMe₃, PBu₃, P(furyl)₃, and the arsine AsPh₃.

(14) Boc-hydrazones were prepared by heating a 1:1 mixture of hydrazide and aldehyde (typically 1 g) in ethanol with 10 drops glacial HOAc at 80 °C for 15 min and then allowing the solution to cool. The hydrazone product can then be isolated by vacuum filtration.

(15) It is necessary for the nucleuphile to have a pK_a ≤ 15 for intermolecular Mitsunobu reactions: Hughes, D. L. The Mitsunobu Reaction. In *Org. Reactions*, John Wiley & Sons: New York, 1993, Vol. 42, p 335–656.

TABLE 2. Mitsunobu Reaction of Boc-Hydrazones with Benzyl Alcohol

Compound	Hydrazone	Reaction time (hours)	Yield (%)[a]
-		3	NR
17		3	20
18		3	37
19		3	61
20		3	71

[a] Reactions were run with 100 mg of hydrazone; all yields are post silica gel column chromatography.

progressing. Concentrating the reacting mixture to dryness and chromatographing the residue (EtOAC/Hexanes) gives the pure product.

Procedure B: To a round-bottomed flask are added triphenylphosphine (2.0 equiv) and THF (0.4 M relative to hydrazone substrate) and the mixture is cooled to 0 °C (ice bath). Once cool, the solution is treated with DBAD (1.8 equiv) and the mixture stirred for 10 min, during which time the phosphine-DBAD adduct precipitates. To the slurry/solid mass is then added, dropwise over 10 min, a solution consisting of hydrazone, alcohol (1.5 equiv), and THF (0.4 M). The resultant mixture is stirred at 0 °C until reaction is complete or stops progressing.

Procedure C: As per procedure A except DEAD was used.

Procedure D: As per procedure B except DEAD was used.

Procedure E: To a round-bottomed flask are added triphenylphosphine (2.0 equiv) and THF (0.4 M relative to hydrazone substrate) and the mixture is cooled to 0 °C (ice bath). Once cool, the solution is treated with DEAD (1.8 equiv) and the mixture stirred for 10 min before adding, dropwise over 3 min, a solution consisting of the hydrazone and THF (0.7 M). After 10 min, a solution consisting of alcohol (1.5 equiv) and THF (0.7 M relative to hydrazone) is added dropwise over 3 min. The reaction is then stirred at 0 °C (ice bath) until complete.

Procedure F: To a round-bottomed flask are added triphenylphosphine (2.0 equiv) and THF (0.4 M relative to hydrazone substrate) and the mixture is cooled to 0 °C (ice bath). Once cool, the solution is treated with DEAD (1.8 equiv) and the mixture stirred for 10 min before adding, dropwise over 3 min, a solution consisting of the alcohol (1.5 equiv) and THF (0.7 M relative to the hydrazone). After 10 min, a solution consisting of hydrazone and THF (0.7 M relative to hydrazone) is added dropwise over 3 min. The reaction is then stirred at 0 °C (ice bath) until complete.

3: white solid; mp 154−156 °C, vigorous decomposition; ^{1}H NMR (acetone-d_6, 600 MHz) δ 11.10−11.97 (m, 1H), 9.13−8.93 (m, 1H), 7.90−7.85 (m, 2H), 7.70−7.63 (m, 5H), 2.39 (s, 3H), 1.53−1.50 (m, 4H), 1.47 (s, 7H), 1.35 (s, 7H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 160.2, 153.7, 145.8, 143.4, 138.4, 134.4, 132.0, 131.4, 130.4, 129.6, 128.5, 84.7, 84.5, 28.3,

28.0, 21.5; MS (TOF) *m/z* 505.0824 [M + H]; HRMS calcd for $C_{24}H_{32}O_6N_4S$ 505.2115, found 505.2093 [M + H].

4: white solid; mp 109−110 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.94−7.90 (m, 2H), 7.75−7.71 (m, 1H), 7.59−7.55 (m, 2H), 7.48−7.41 (m, 4H), 7.40−7.33 (m, 5H), 7.32−7.26 (m, 1H), 5.04−5.00 (m, 2H), 2.44−2.40 (m, 3H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 146.4, 146.2, 138.0, 137.2, 136.3, 131.8, 131.5, 130.6, 130.5, 130.0, 129.4, 128.9, 128.7, 52.9, 22.5; MS (ESI) *m/z* 365.3 [M + H]; HRMS calcd for $C_{21}H_{20}N_2O_2S$ 365.1318, found 365.1312 [M + H].

5: white solid; mp 73−74 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.08 (s, 1H), 7.80 (d, $J = 8.2$ Hz, 2H), 7.71−7.66 (m, 2H), 7.42−7.38 (m, 3H), 7.30 (d, $J = 8.1$ Hz, 2H), 3.54 (d, $J = 6.5$ Hz, 2H), 2.40 (s, 3H), 1.10−1.01 (m, 1H), 0.59−0.55 (m, 2H), 0.43−0.38 (m, 2H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 148.9, 143.7, 134.5, 134.0, 130.2, 129.3, 128.5, 128.1, 127.4, 52.5, 21.4, 9.3, 4.3; MS (ESI) *m/z* 329.3 [M + H]; HRMS calcd for $C_{18}H_{20}N_2O_2S$ 329.1318, found 329.1305 [M + H].

6: white solid; mp 101−103 °C; ^{1}H NMR (CDCl₃, 500 MHz) δ 7.88 (d, $J = 8.3$ Hz, 2H), 7.81 (s, 1H), 7.70−7.66 (m, 2H), 7.43−7.38 (m, 3H), 7.28 (d, $J = 8.2$ Hz, 2H), 4.68 (s, 2H), 2.39 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (CDCl₃, 500 MHz) δ 144.9, 144.0, 134.4, 133.9, 129.9, 129.3, 128.6, 128.4, 127.2, 96.1, 92.2, 36.6, 21.4, −0.64; MS (ESI) *m/z* 385.2 [M + H]; HRMS calcd for $C_{20}H_{24}N_2O_2$-SSi 385.1400, found 385.1386 [M + H].

7: white solid; mp 52−55 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.17 (s, 1H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.72−7.69 (m, 2H), 7.45−7.40 (m, 5H), 4.19−4.01 (m, 1H), 3.90−3.73 (m, 4H), 3.70−3.65 (m, 1H), 3.46 (td, $J = 2.9, 11.7$ Hz, 1H), 3.02−2.67 (m, 2H), 2.40 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 155.9, 146.0, 136.6, 136.3, 131.9, 131.3, 130.5, 129.2, 80.9, 75.5, 68.1, 52.3, 48.1, 46.8, 44.8, 43.6, 29.5, 22.4; MS (ESI) *m/z* 496.3 [M + Na]; HRMS calcd for $C_{24}H_{31}N_3O_5S$ 474.2057, found 474.2063 [M + H].

8: white solid, mp 103−104 °C; ^{1}H NMR (CDCl₃, 600 MHz) δ 8.31 (s, 1H), 7.69 (d, $J = 8.3$ Hz, 4H), 7.46−7.39 (m, 3H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.98 (s, 1H), 4.93 (d, $J = 5.9$ Hz, 1H), 4.68 (d, $J = 5.9$ Hz, 1H), 4.30−4.26 (m, 1H), 3.77−3.72 (m, 1H), 3.38−3.34 (m, 1H), 3.36 (s, 3H), 2.42 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (CDCl₃, 600 MHz) δ 156.4, 144.3, 133.5, 131.1, 129.6, 128.7, 128.3, 128.1, 112.4, 109.9, 85.1, 83.6, 82.3, 55.2, 52.7, 26.3, 24.8, 21.6; MS (ESI) *m/z* 483.3 [M + Na]; HRMS calcd for $C_{23}H_{28}N_2O_6S$ 461.1741, found 461.1724 [M + H].

9: white solid; mp 98−100 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.54−8.50 (m, 1H), 8.38−8.35 (m, 1H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 1H), 7.66−7.63 (m, 1H), 7.50−7.46 (m, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.25−7.20 (m, 4H), 4.92 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 150.8, 150.7, 148.2, 146.4, 136.8, 136.6, 136.1, 133.6, 132.0, 131.6, 130.6, 130.1, 129.1, 125.4, 50.9, 22.5; MS (ESI) *m/z* 366.3 [M + H]; HRMS calcd for $C_{20}H_{19}N_3O_2S$ 366.1271, found 366.1265 [M + H].

10: white solid; mp 105−106 °C; ^{1}H NMR (CDCl₃, 600 MHz) δ 7.85 (d, $J = 8.3$ Hz, 2H), 7.73 (s, 1H), 7.61−7.57 (m, 2H), 7.38−7.35 (m, 3H), 7.33 (d, $J = 8.4$ Hz, 2H), 7.21−7.20 (m, 1H), 4.98 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (CDCl₃, 600 MHz) δ 151.2, 145.7, 144.4, 136.2, 134.4, 133.8, 130.2, 129.6, 128.6, 128.2, 127.4, 120.5, 47.7, 21.6; MS (ESI) *m/z* 450.0 [M + H]; HRMS calcd for $C_{18}H_{16}$-BrN₃O₂S₂ 449.9940, found 449.9930 [M + H].

11: white solid; mp 127−128 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.45 (s, 1H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.66−7.63 (m, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.43−7.40 (m, 3H), 5.02 (s, 2H), 3.89 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (CDCl₃, 600 MHz) δ 150.4, 145.6, 144.2, 135.0 (d, $J = 15.9$ Hz), 131.3, 130.6, 129.7, 129.3, 128.4, 115.7, 106.3, 46.5, 33.9, 21.5; MS (ESI) *m/z* 524.9 [M + H]; HRMS calcd for $C_{19}H_{18}Br_2N_4O_2S$ 524.9590, found 524.9575 [M + H].

12: colorless oil; ^{1}H NMR (CDCl₃, 600 MHz) δ 8.62 (s, 1H), 7.74−7.71 (m, 2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.45−7.39 (m, 3H),

7.27 (d, J = 8.3 Hz, 2H), 4.50 (heptet, J = 6.7 Hz, 1H), 2.39 (s, 3H), 1.08 (d, J = 6.7 Hz, 6H); ^{13}C NMR (CDCl$_3$, 600 MHz) δ 159.3, 143.7, 136.1, 134.1, 130.9, 129.6, 128.7, 128.0, 127.9, 53.0, 21.5, 20.5; MS (ESI) m/z 317.3 [M + H]; HRMS calcd for C$_{17}$H$_{20}$N$_2$O$_2$S 317.1318, found 317.1317 [M + H].

13: colorless oil; ^{1}H NMR (CDCl$_3$, 600 MHz) δ 8.72 (s, 1H), 7.74 (d, J = 6.8 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.47−7.40 (m, 3H), 7.27 (d, J = 8.1 Hz, 2H), 4.54−4.48 (m, 1H), 2.41 (s, 3H), 1.67−1.61 (m, 2H), 1.59−1.51 (m, 4H), 1.44−1.37 (m, 2H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 163.9, 146.0, 137.4, 136.0, 133.1, 131.4, 130.7, 130.1, 130.0, 63.7, 31.3, 26.4, 22.5; MS (ESI) m/z 343.3 [M + H]; HRMS calcd for C$_{19}$H$_{22}$N$_2$O$_2$S 343.1475, found 343.1479 [M + H].

14: white solid; mp 143−145 °C; ^{1}H NMR (CDCl$_3$, 600 MHz) δ 8.57 (s, 1H), 7.71 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 7.1 Hz, 2H), 7.42−7.39 (m, 1H), 7.37−7.30 (m, 4H), 7.11−7.06 (m, 4H), 5.03 (quintet, J = 8.2 Hz, 1H), 3.09−3.03 (m, 2H), 2.98−2.92 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (CDCl$_3$, 600 MHz) δ 161.7, 144.2, 140.6, 134.9, 133.6, 131.2, 129.6, 128.6, 128.2, 126.5, 124.2, 61.0, 36.1, 21.6; MS (ESI) m/z 391.3 [M + H]; HRMS calcd for C$_{23}$H$_{22}$N$_2$O$_2$S 391.1475, found 391.1467 [M + H].

15: colorless oil; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.54 (s, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.75 (d, J = 6.9 Hz, 2H), 7.51−7.44 (m, 5H), 5.89−5.74 (m, 1H), 5.40−5.25 (m, 1H), 4.90 (br s, 1H), 4.01−3.83 (m, 2H), 3.82−3.63 (m, 1H), 3.45−3.30 (m, 1H), 2.45 (s, 3H), 1.45−1.36 (m, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 155.9, 146.4, 137.8, 136.0, 132.9, 131.7, 130.6, 129.9 (d, J = 19.7 Hz), 81.1, 56.9, 45.2, 43.1, 29.5, 22.5; MS (ESI) m/z 478.3 [M + Na]; HRMS calcd for C$_{24}$H$_{29}$N$_3$O$_4$S 456.1952, found 456.1934 [M + H].

16: white solid; mp 149−150 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.68 (s, 1H), 7.81−7.78 (m, 4H), 7.51−7.43 (m, 5H), 4.33−4.27 (m, 1H), 4.14−3.98 (m, 2H), 2.92−2.69 (m, 2H), 2.43 (s, 3H), 1.74−1.66 (m, 2H), 1.57−1.51 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 161.0, 155.9, 146.3, 138.4, 136.1, 133.0, 131.7, 130.7, 129.8, 80.5, 60.8, 31.9, 29.5, 22.5; MS (ESI) m/z 349.2 [M − BOC]; HRMS calcd for C$_{24}$H$_{31}$N$_3$O$_4$S 458.2108, found 458.2099 [M + H].

17: colorless oil; ^{1}H NMR (CDCl$_3$, 600 MHz) δ 7.70 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.36−7.34 (m, 2H), 7.28−

7.24 (m, 1H), 7.23 (d, J = 7.4 Hz, 2H), 5.15 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (CDCl$_3$, 600 MHz) δ 153.3, 138.4, 135.5, 131.0 (quartet, J = 32.3 Hz), 128.9, 127.4, 127.1, 126.2, 125.5 (quartet, J = 3.7 Hz), 124.9, 123.1, 82.4, 48.6, 28.2; MS (ESI) m/z 323.3 [M + H]; HRMS calcd for C$_{20}$H$_{21}$F$_3$N$_2$O$_2$ 379.1628, found 379.1635 [M + H].

18: white solid; mp 56−57 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.08 (d, J = 7.9 Hz, 1H), 7.93 (br s, 1H), 7.55−7.48 (m, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.24−7.20 (m, 2H), 7.16 (d, J = 7.5 Hz, 2H), 7.13 (t, J = 7.3 Hz, 1H), 5.08 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 155.2, 137.8, 137.1, 135.2, 134.2, 130.9, 130.6, 129.2, 128.6, 128.4, 127.4 (quartet, J = 5.8 Hz), 127.1, 125.3, 83.3, 50.0, 29.4; HRMS calcd for C$_{20}$H$_{21}$F$_3$N$_2$O$_2$ 379.1628, found 379.1614 [M + H].

19: yellow foam; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.28 (br s, 1H), 8.14 (dd, J = 1.3, 8.0 Hz, 1H), 7.95 (dd, J = 1.1, 8.2 Hz, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.60−7.56 (m, 1H), 7.40−7.35 (m, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 5.23 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 155.0, 150.2, 137.8, 136.7, 134.8, 131.3, 130.5, 129.7, 129.1, 128.5, 126.2, 83.3, 49.8, 29.3; MS (ESI) m/z 378.3 [M + Na]; HRMS calcd for C$_{19}$H$_{21}$N$_3$O$_4$ 356.1605, found 356.1593 [M + H].

20: orange crystalline solid; mp 108−109 °C; ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.20 (d, J = 7.8 Hz, 2H), 8.47 (br s, 1H), 7.83 (t, J = 8.4 Hz, 1H), 7.39−7.36 (m, 2H), 7.29−7.26 (m, 3H), 5.18 (s, 2H), 1.55 (s, 9H); ^{13}C NMR (acetone-d_6, 600 MHz) δ 154.8, 151.5, 137.3, 132.9, 132.2, 130.5, 129.9, 129.1, 128.2, 125.9, 83.7, 49.4, 29.3; MS (ESI) m/z 423.7 [M + Na]; HRMS calcd for C$_{19}$H$_{20}$N$_4$NaO$_6$ 423.1281, found 423.1275 [M + Na].

Supporting Information Available: ^{1}H and ^{13}C NMR data for all prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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