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A GENERAL AND EFFICIENT METHOD FOR SYNTHESIS OF FUNCTIONALIZED ETHYLENEDIAMINE DERIVATIVES

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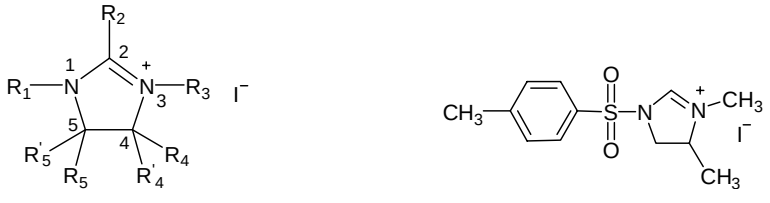
Abstract–Reaction of tetrahydrofolate model, 1-tosyl-3,4-dimethylimidazolinium iodide (**1**), and a series of aromatic or aliphatic amines produced *N,N,N′*-trisubstituted-2-methylethylenediamine derivatives (**2-10**) in good to excellent yields through a nucleophilic addition and the followed ring-opening mechanism. The coenzyme model was proved to be more electrophilic than those reported before.

INTRODUCTION

Tetrahydrofolate (THF) was responsible for transfer of one-carbon fragment in the biological synthesis and metabolism.[1] Thus the study on the THF coenzyme model (Figure 1a) may provide a valuable class of reagents for group transfer reactions for practical utility.[2,3] In our earlier research, a series of 1-aryl-4,5-dihydroimidazolium iodides and 1-arylsulfonyl-4,5-dihydroimidazolium iodides had been synthesized as the THF coenzyme model to improve their potential in one-carbon unit transfer reactions.[4-7,12] One important approach was to adjust the basicity of *N*(1) and *C*(2) in the imidazolinium unit by using different substituted groups.[4,5] *N*(1)-Arylsulfonyl substituted models showed the higher reactivity than those *N*(1)-aryl substituted ones, and *C*(2)-methyl substituted models were superior to those *C*(2)-phenyl substituted ones. Consequently, we presumed that the reactivity of our THF coenzyme models could obviously be affected by the steric hindrance on *C*(2) and induced effect in *N*(1).[6-9]



(a) (b)

Figure 1 (a) General THF models. (b) 1-Tosyl-3,4-dimethylimidazolinium iodide (**1**).

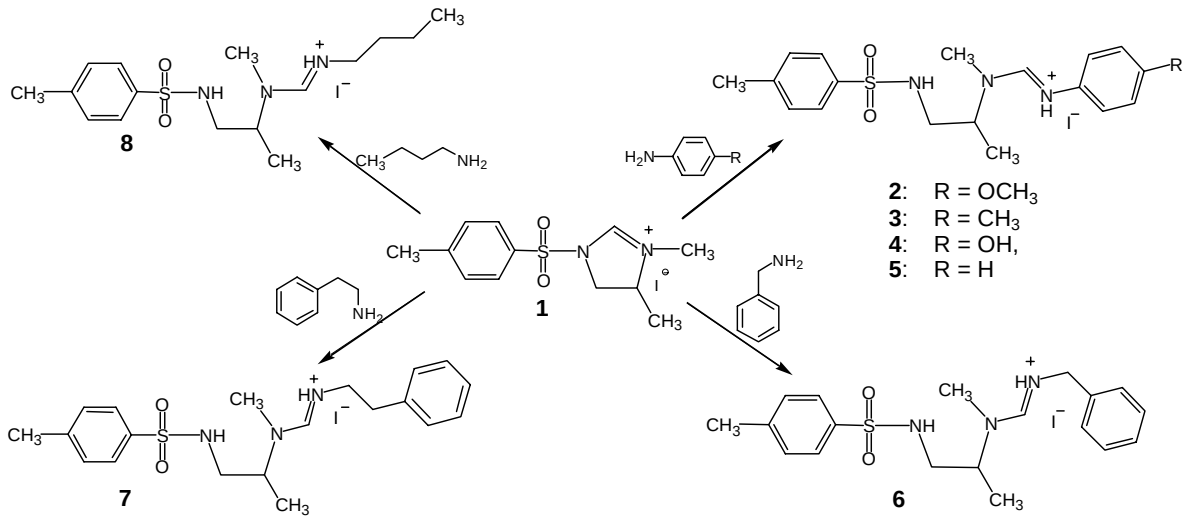
Furthermore, despite of *N*(1) and *C*(2), we wanted to know if the substituted groups in *C*(4) and *C*(5) were additional important factor on the reactivity of the THF models. We noted that in the literatures, 1-tosyl-3,4,4-trimethylimidazolinium iodide showed the higher reactivity than 1-tosyl-3,4,4,5,5-pentamethylimidazolinium iodide.[10] So we extrapolated that if the substituted groups of *C*(4) and *C*(5) in imidazolium unit were H atoms, the electrophilic ability of *C*(2) would be further improved. However, the compound was difficult to prepare and not easy to handle due to its high instability under atmospheric conditions.[10]

These considerations prompted us to synthesize our new model, 1-tosyl-3,4-dimethylimidazolinium iodide (**1**) (Figure 1b), and attempt its reactivity with a series of different carbon nucleophilic reagents.[11] In this work, we hope to extend its scope to a series of different nitrogen nucleophilic reagents. The present research showed that model (**1**) was be more electrophilic than those reported before and provided a convenient and high-yield method to prepare functionalized ethylenediamine derivatives**,** and may enable chemical and biological studies on these derivatives, which will be used in pharmaceutical research.[12]

RESULTS AND DISCUSSION

4,5-Dihydroimidazolium salts were commonly believed not active enough toward amino nucleophiles, especially aromatic amine. 2,3-Diarylimidazolinium salts could only react with primary aliphatic amines.[6-9] But 1-tosyl-3,4-dimethylimidazolinium iodide (**1**)**,** which had an unique resonance *C*(2) cation center between *N*(1) and *N*(3) in its imidazolinium ring, so it became more susceptible to amino nucleophilic attack than 2,3-diarylimidazolinium salts. We found that model (**1**) could react not only with aliphatic amines but also with aromatic amines, and afforded ring-opened products (**2-8**) (Scheme 1).

Scheme 1



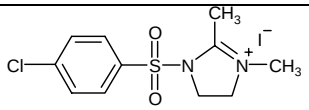
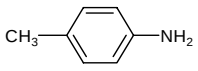
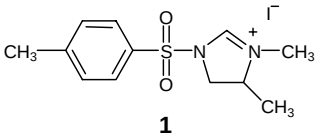
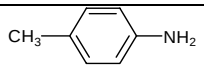
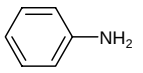
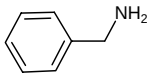
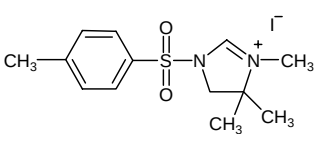
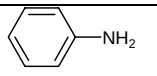
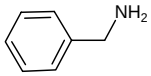
When 1-tosyl-3,4-dimethylimidazolinium iodide (**1**) was treated with a series of amines, the corresponding *N*,*N*,*N*′-trisubstituted 2-methylethylenediamine derivatives (**2-8**) were produced in the yields of 72–98% (Table 1). The reaction were refluxed in acetonitrile, and the reflux time was dependent on the nucleophilic activity of amines, generally from 0.5 to 2 h. Reaction were easily followed by TLC and workout was straightforward. However, they remained unchanged even with longer reflux time when aromatic amines have an electron-withdrawing group, such as *p*-chloroaniline, *p*-nitroaniline. Compared with the earlier results,[10,13] as shown in Table 2, the model compound (**1**) was proved to be more electrophilic under the same conditions.

Table 1 Nucleophilic Addition of Model Compound (**1**) with Amines[a]

Product	Reagent	Temperature	Time (h)	Yield (%)
2	*p*-anisidine	rt	0.5	96
3	*p*-toluidine	rt	0.5	98
4	*p*-aminophenol	reflux	4	83
5	aniline	reflux	4	86
6	benzylamine	reflux	1	75
7	phenethylamine	reflux	1	72
8	*n*-butylamine	reflux	0.25	89
	p-chloroaniline	reflux	24	N R[b]
	p-nitroaniline	reflux	24	N R[b]

[a] All reactions were performed in acetonitrile. [b] No reaction.

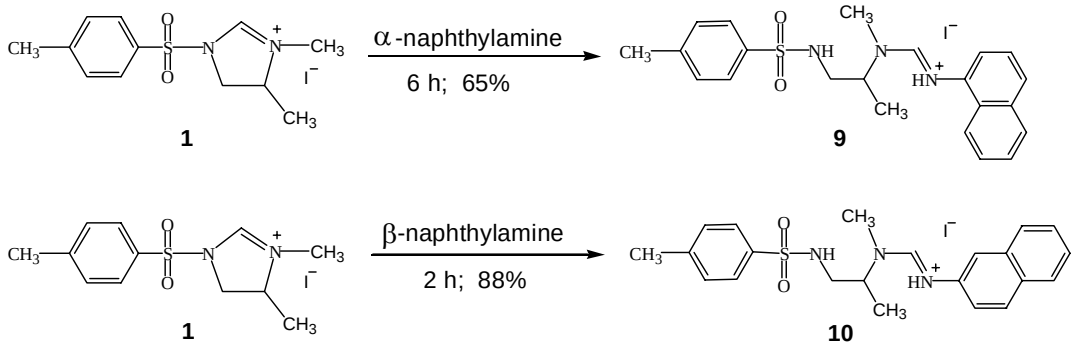
Table 2 Comparison of Model Compound (**1**) with the Other Models Reported Before [a]

THF Models	Reagent	Temperature	Time (h)	yield (%)
		reflux	4	98[13]
 **1**		rt	0.5	98
		reflux	4	86
		reflux	1	75
		reflux	overnight	no report[10]
		reflux	overnight	64[10]

[a] All reactions were performed in acetonitrile.

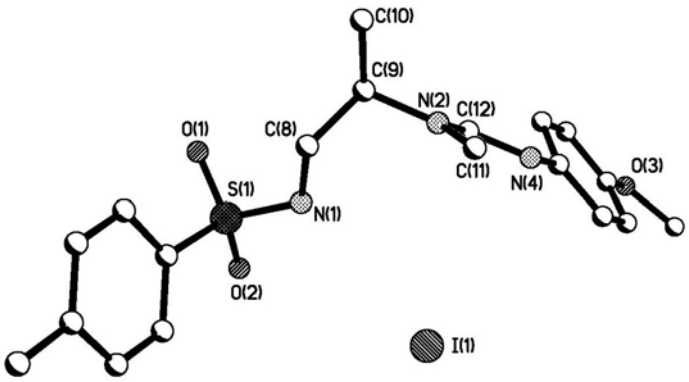
In terms of the good reaction abilities of model compound (**1**) with aniline derivatives, we further attempted the reactions of model compound (**1**) with more hindered naphthylamines in the same conditions. So *α*-naphthylamine and *β*-naphthylamine were used to react with 1-tosyl-3,4-dimethylimidazolinium iodide (**1**), providing the *N*,*N*,*N*′-trisubstituted 2-methylethylenediamine derivatives (**9**) and (**10**) in 65% and 88% yields, respectively (Scheme 2).

Scheme 2



All the above products were identified by IR, ^{1}HNMR, EI-MS and elemental analysis. The structure of compound (**2**) could further been demonstrated by X-Ray spectra. It was observed that *C*11, *N*2, *C*12 and *N*4 were almost coplanar and the length of *C*12---*N*2 and *C*12---*N*4 were 1.300(4) Å and 1.309(5) Å, respectively, which were much shorter than standard single *C*---*N* bond [Lide (1962) pointed out that the standard single and doubled *C*---*N* bond lengths are 1.474 and 1.265 Å], suggesting that positive charge delocalized among *N*4---*C*12---*N*2.

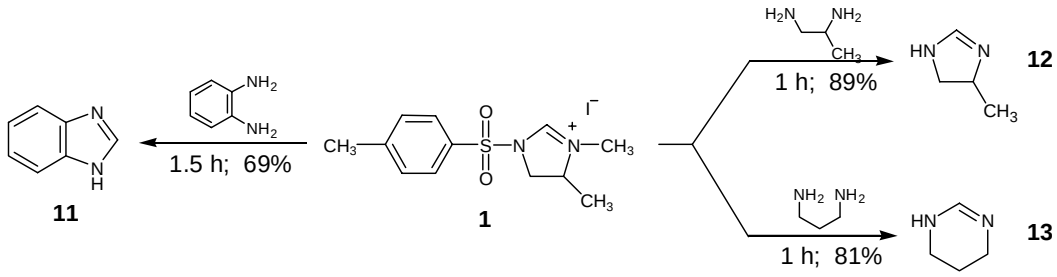
Figure 2 X-Ray structure of compound (**2**)



Also, we tested the action of one-carbon transfer of model compound (**1**) with several bifunctional nucleophiles in above condition (Scheme 3). When model compound (**1**) was treated with 1,2-diaminopropane, 1,3-diaminopropane and *o*-phenylenediamine, the corresponding transfer productions (**11-13**) were obtained in the yields of 69-89%. The known productions (**11-13**) shown in

Scheme 3 were confirmed by IR and 300 MHz ^{1}H NMR analyses. These simple reactions demonstrated that one-carbon unit in model compound (**1**) can be transferred easily to suitable acceptors at mild conditions.

Scheme 3



In conclusion, 1-tosyl-3,4-dimethylimidazolinium iodide (**1**) reacted smoothly with a series of aromatic and aliphatic amines to provide the *N*,*N*,*N*′-trisubstituted 2-methylethylenediamine derivatives (**2-10**) in good to excellent yields through a nucleophilic addition and the followed ring-opening mechanism. Further, the model compound also showed good reactivity for the one-carbon transfer with several diamines. The THF model was proved to be the more active than those reported before. Especially, the present research provided a convenient and high-yield method to prepare functionalized ethylenediamine derivatives**,** and may enable chemical and biological studies on these derivatives, which will be used in pharmaceutical research.[12]

EXPERIMENTAL

MS spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75MHz, respectively, with TMS as a spectra standard. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. IR spectra were obtained on a Shimadzu IR-1700 spectrometer. X-Ray data were collected on a Bruker AXS SMART APEX CCD diffractometer, using Mo-Kα radiation (λ = 0.71073 Å). The TLC was carried out on silica get GF-254 20*20 cm^2 plate. Melting points were uncorrected. All reactions were performed under an inert atmosphere of nitrogen, all reagents and solvents were purified and dried as required.

General procedure for the reaction of model compound (1) with aromatic amines:

A solution of 1-Tosyl-3,4-dimethylimidazolinium iodide (**1**) (0.38 g, 1 mmol) and aromatic amines (1 mmol) in 10 mL of anhydrous acetonitrile was refluxed or stirred in rt for 0.5-2 h, white solids (**2-10**) were observed. The white solids were collected and recrystallized from dry ethyl alcohol to afford white crystals (**2-10**).

Compound (***2***): yield (96%) as white crystal, mp 222-223 ^{o}C. ^{1}H-NMR (300 MHz, δ ppm, DMSO-d_6): 1.22 (d, *J* = 6.48, 3H), 2.35 (s, 3H), 2.97 (s, 3H), 3.03 (m, 1H), 3.34 (s, 2H), 3.76 (s, 3H), 3.99 (br, 1H), 7.04-7.07 (d, *J* = 8.64, 2H), 7.36 (t, 4H), 7.65-7.67 (d, *J* = 7.89, 2H), 7.87 (m, 1H), 8.52 (br, 1H); IR

(KBr) cm^{-1}: 3424(m), 3120, 1686(m), 1631, 1596, 1515, 1325, 1159, 832; MS *m/z*: 376 (M-I), 254, 155, 108, 99; *Anal*. Calcd for $C_{19}H_{26}N_3O_3IS$: C, 45.33; H, 5.21; N, 8.35. Found C, 45.44; H, 5.30; N, 8.31.

*Compound (**3**)*: yield (98%) as white crystal, mp 210-212 ^oC. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.27 (d, *J* = 6.72, 3H), 1.58 (s, 6H), 2.25 (s, 2H), 2.33 (s, 1H), 2.41 (s, 3H), 4.45 (br, 1H), 7.09-7.80 (m, 9H), 8.81 (br, 1H); IR (KBr) cm^{-1}: 3415(m), 3104, 1687(m), 1630, 1598, 1501, 1342, 1159, 833; MS m/z: 360 (M-I), 278, 246, 127, 99; Anal. Calcd for $C_{19}H_{26}N_3O_2IS$: C, 46.82; H, 5.38; N, 8.62. Found C, 46.80; H, 5.62; N, 8.44.

Compound (***4***): yield (83%) as white crystal, mp 97.1-99.8 ^oC. ^1H-NMR (300 MHz, δ ppm, DMSO-d_6): 1.22 (d, *J* = 6.42, 3H), 2.36 (s, 3H), 2.96 (m, 5H), 3.33 (s, 1H), 3.97 (br, 1H), 6.86 (d, *J* = 8.19, 2H), 7.22 (d, *J* = 8.16, 2H), 7.39 (d, *J* = 7.80, 2H), 7.68 (d, *J* = 7.71, 2H), 8.61 (br, 1H), 8.62 (s, 1H), 9.69 (s, 1H); IR (KBr) cm^{-1}: 3410, 3247, 1685, 1631, 1516, 1326, 1158, 834, 755; MS m/z: 362 (M-I), 155, 127, 108, 99; Anal. Calcd for $C_{18}H_{24}N_3O_3IS$: C, 44.18; H, 4.94; N, 8.57. Found C, 44.34; H, 4.77; N, 8.66.

Compound (***5***): yield (86%) as white crystal, mp 145.7-147.5 ^oC. ^1H-NMR (300 MHz, δ ppm, DMSO-d_6): 1.26 (d, *J* = 6.42, 3H), 2.37 (s, 3H), 3.13 (m, 5H), 3.35 (s, 1H), 4.06 (br, 1H), 7.41 (m, 6H), 7.52 (d, *J* = 7.29, 2H), 7.91 (m, 1H), 8.64 (s, 1H), 11.04 (br, 1H); IR (KBr) cm^{-1}: 3444, 3045, 1685, 1630, 1597, 1495, 1341, 1161, 834, 759; MS m/z: 346 (M-I), 254, 127, 99, 93; Anal. Calcd for $C_{18}H_{24}N_3O_2IS$: C, 45.67; H, 5.11; N, 8.87. Found C, 45.79; H, 5.19; N, 8.84.

Compound (***6***): yield (75%) as white crystal, mp 130-133 ^oC. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.35 (d, *J* = 6.72, 3H), 2.43 (s, 3H), 2.88 (s, 3H), 3.02-3.29 (m, 5H), 4.27 (br, 1H), 4.80 (br, 1H), 7.38 (m, 5H), 7.57 (d, *J* = 6.99, 2H), 7.81 (d, *J* = 7.80, 2H), 8.74 (s, 1H); IR (KBr) cm^{-1}: 3435, 3088, 1689, 1632, 1598, 1495, 1328, 1160, 834, 750; MS m/z: 361 (M-I), 254, 155, 106, 99; Anal. Calcd for $C_{19}H_{26}N_3O_2IS$: C, 46.82; H, 5.38; N, 8.62. Found C, 46.51; H, 5.40; N, 8.13.

*Compound (**7**)*: yield (72%) as white crystal. mp 112.6-114.2 ^oC.. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$):1.04 (d, *J* = 6.60, 3H), 2.41 (s, 3H), 2.72 (br, 1H), 2.99 (br, 1H), 3.11(m, 6H), 3.63 (m, 1H), 3.91 (s, 2H), 7.30 (m, 7H), 7.55 (d, *J* = 13.83, 1H), 7.78 (d, *J* = 7.92, 2H), 8.81(br, 1H); IR (KBr) cm^{-1}: 3432, 2925, 1692, 1500, 1453, 1400, 1159, 1091; MS m/z: 374(M-I), 254, 155, 127, 99; *Anal*. Calcd for $C_{20}H_{28}N_3O_2IS$: C, 47.91; H, 5.63; N, 8.38. Found C, 47.68; H, 5.70; N, 8.31.

*Compound (**8**)*: yield (89%) as oil. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 0.94 (t, 3H), 1.24 (d, *J* = 6.54, 3H), 1.38 (m, 2H), 1.73 (m, 2H), 2.16 (s, 3H), 2.72 (m, 1H), 3.15 (s, 3H), 3.23 (s, 1H), 3.52 (m, 2H), 4.24 (br, 1H), 7.04 (br, 1H), 7.28 (d, *J* = 7.83, 2H), 7.75 (d, *J* = 7.68, 2H), 8.14 (m, 1H), 8.76 (br, 1H); IR (KBr) cm^{-1}: 3441, 2958, 1694, 1598, 1495, 1433, 1387, 1248, 1159, 1091; MS m/z: 326(M-I), 254, 155, 127, 99.

Compound (***9***): yield (65%) as white crystal, mp 109.2-111.7 ^oC. ^1H-NMR (300 MHz, δ ppm, DMSO-d_6): 1.24 (d, *J* = 6.12, 3H), 2.34 (s, 3H), 2.97 (m, 2H), 3.34 (s, 3H), 3.96 (s, 1H), 7.37 (d, *J* = 7.59, 2H),

7.43-8.18 (m, 10H), 8.44 (s, 1H), 11.37 (br, 1H); IR (KBr) cm^{-1}: 3432, 3056, 1682, 1628, 1598, 1493, 1398, 1159, 834, 753; MS m/z: 254, 155, 142, 127, 99; Anal. Calcd for $C_{22}H_{26}N_3O_2IS$: C, 50.48; H, 5.01; N, 8.06. Found C, 50.28; H, 4.76; N, 8.15.

Compound (***10***): yield (88%) as white crystal, mp 193-195 ^oC. ^1H-NMR (300 MHz, δ ppm, DMSO-d_6): 1.26 (d, *J* = 6.36, 3H), 2.34 (s, 3H), 3.01 (m, 5H), 4.11 (s, 1H), 7.40 (d, *J* = 7.80, 2H), 7.52-8.10 (m, 10H), 8.83 (d, *J* = 9.93, 1H), 11.24 (br, 1H); IR (KBr) cm^{-1}: 3416, 3123, 1688, 1631, 1523, 1494, 1318, 1153, 833, 743; MS m/z: 395 (M-HI), 254, 155, 143, 127, 99; Anal. Calcd for $C_{22}H_{26}N_3O_2IS$: C, 50.48; H, 5.01; N, 8.06. Found C, 50.20; H, 5.08; N, 8.26.

General procedure for the reaction of model compound (1) with diamines:

A solution of 1-Tosyl-3,4-dimethylimidazolinium iodide (**1**) (1 mmol) and diamine (1 mmol) in 10 mL of anhydrous acetonitrile was refluxed for 1-1.5 h. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, gradient chloroform and methanol).

*Compound (**11**)*: Yield (69%) as white crystals (water), mp 171.2^{o}C-173.0 ^{o}C. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 7.31 (m, 2H), 7.67 (br, 2H) 8.10 (s, 1H), 10.21 (br, 1H); IR (KBr) cm^{-1}: 3114, 3038, 2862, 1620, 1602, 1587, 1495, 1459, 1246.

*Compound (**12**)*: Yield (89%) as yellow oil. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.12 (d, J=6.27, 3H), 3.08 (m, 1H), 3.65 (m, 1H), 3.84 (m, 1H), 4.17 (s, 1H), 6.96 (s, 1H); IR (KBr) cm^{-1}: 3185, 2962, 1651, 1599, 1454, 1377, 969.

*Compound (**13**)*: Yield (81%) as colorless oil. ^1H-NMR (300 MHz, δ ppm, $CDCl_3$): 1.69 (m, 2H), 3.14 (t, 4H), 5.12 (br, 1H), 7.00 (s, 1H); IR (KBr) cm^{-1}: 3284, 2945, 1680, 1640, 1382.

Crystal data for compound (2):

Empirical formula: $C_{19}H_{26}N_3O_3IS$, crystal size: 0.30×0.10×0.10, Triclinic, a = 6.3635(12)Å, b = 13.284(2)Å, c = 14.331(3)Å, α = 62.898(2)°, β = 81.682(2)°, γ = 87.939(2)°, V = 1066.5(3), T = 293(2)K, space group P-1, Z = 2, d_{calc} = 1.568 g/cm^3, F(000) = 508, 4423 reflections measured, 3686 unique (R_{int}= 0.0178). The final R1 = 0.0349($I > 2\sigma$), 0.04161(all data), wR2 = 0.0740($I > 2\sigma$), 0.0763(all data).

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