HETEROCYCLES, Vol. 92, No. 11, 2016, pp. 2047 - 2058. © 2016 The Japan Institute of Heterocyclic Chemistry
Received, 7th August, 2016, Accepted, 28th September, 2016, Published online, 14th October, 2016
DOI: 10.3987/COM-16-13551

FACILE SYNTHESIS OF IMIDAZO[1,5-*a*]PYRAZIN-8(7*H*)-ONES FROM MESOIONIC 1,3-OXAZOLIUM-5-OLATES VIA A MULTISTEP ONE-POT TRANSFORMATION

Ryosuke Saijo,[a] Hidemitsu Uno,[b] and Masami Kawase[a]*

[a]Faculty of Pharmaceutical Sciences, Matsuyama University, 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan, [b]Department of Chemistry and Biology, Graduate School of Science and Engineering, Ehime University, Matsuyama, 790-8577, Japan; E-mail: kawase@cc.matsuyama-u.ac.jp

Abstract – A novel one-pot conversion of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates into imidazo[1,5-*a*]pyrazin-8(7*H*)-ones by the reaction with TosMIC is described. The structure of the product was determined by single-crystal X-ray analysis.

The imidazo[1,5-*a*]pyrazine **A** has a five-membered imidazole and a six-membered pyrazine ring with a bridgehead nitrogen atom (Figure 1) and is one of the less known members of the azaindolizine family.[1] On the other hand, the isomer imidazo[1,2-*a*]pyrazine **B** is a well-known scaffold in organic synthesis and drug development.[2] These imidazopyrazines have recently been attracting considerable interest because they represent promising building blocks with potential pharmaceutical applications.[1,2]

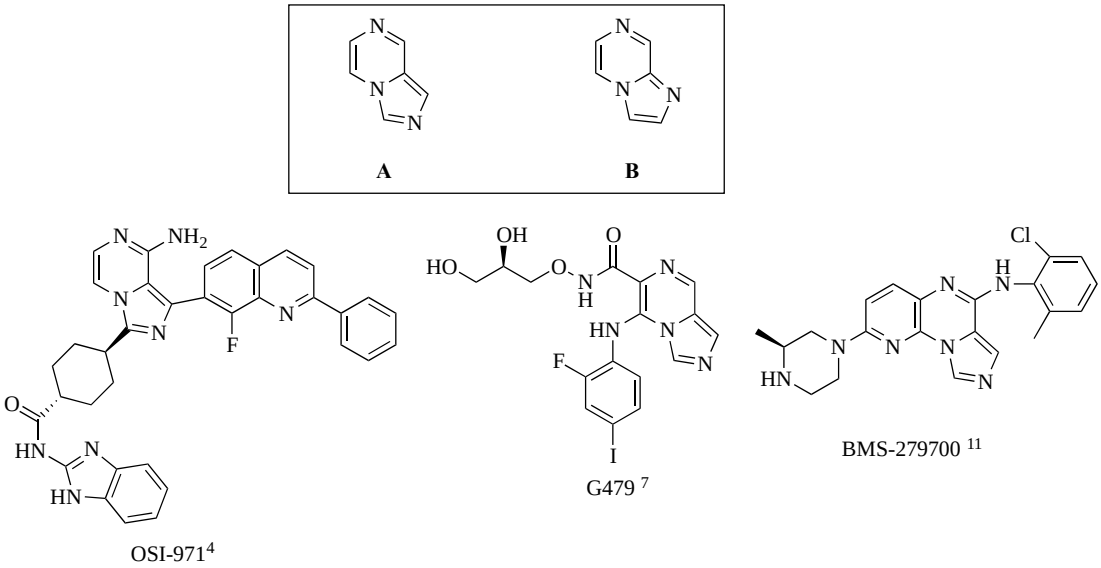
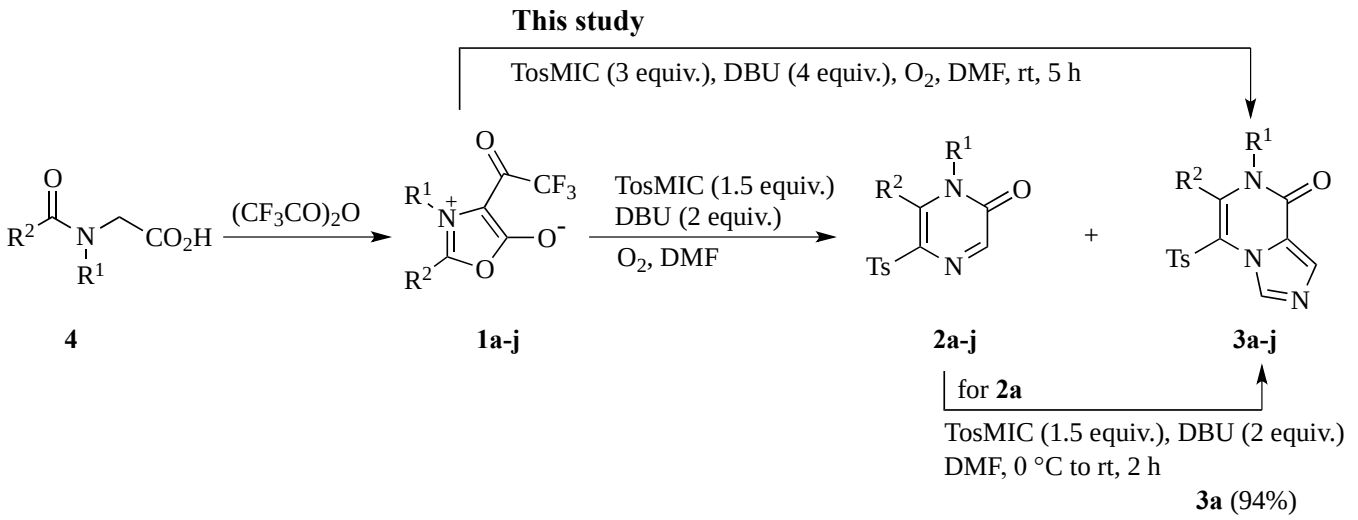


Figure 1. Bioactive imidazo[1,5-*a*]pyrazines

Substituted imidazo[1,5-*a*]pyrazine compounds (Figure 1) have shown many interesting biological activities as, for example, Factor Xa,[3] insulin-like growth-factor-I receptor (IGF-IR),[4] mammalian target of rapamycin (mTor),[5] activated Cdc42-associated kinase (ACK1),[6] MAPK/ERK kinase (MEK),[7] and Bruton's tyrosine kinase (BTK) inhibitors,[8] as well as Corticotropin releasing hormone receptor ligands[9] and smoothened (Smo) antagonists.[10] Recently, the compound BMS-279700 has been identified as a potent inhibitor of the Src-family kinase $p56^{Lck}$ with excellent *in vivo* anti-inflammatory activity.[11] These reports suggest the critical role of imidazo[1,5-*a*]pyrazines in medicinal chemistry and requirement of easy route for the synthesis of substituted imidazo[1,5-*a*]pyrazine derivatives.

Two approaches have been mainly reported in literature for the construction of the imidazo[1,5-*a*]pyrazine ring system. The first approach involves the formation of an imidazole ring by ring closure onto an existing (appropriately substituted) pyrazine intermediate.[12] In the second approach, an appropriately substituted imidazole is annulated by a pyrazine ring formation, which is the much lesser known route.[13] Whereas these approaches have proven very useful for the synthesis of imidazo[1,5-*a*]pyrazines, they generally involve multistep synthetic operations and lack the possibility to generate diversity. Indeed, the development of efficient and general access to functionalized imidazo[1,5-*a*]pyrazines is of great interest.



Scheme 1

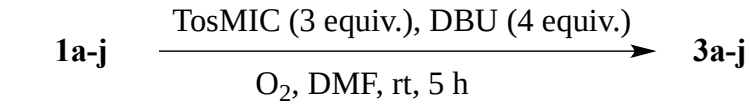
We have previously reported that the unexpected reaction of mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates **1a-h** with *p*-toluenesulfonylmethyl isocyanide (TosMIC) proceeds *via* an initial attack of TosMIC anions on the C-2 position of the ring followed by auto-oxidation to afford pyrazin-2(1*H*)-ones **2a-h** in good yields (Scheme 1).[14] In these reactions, we noticed the formation of imidazo[1,5-*a*]pyrazin-8(7*H*)-ones **3a-h** as a side product, which could be produced by the action of excess TosMIC during reaction. This finding prompted us to investigate the

reaction of **1** with TosMIC more closely and to make it more efficient method for synthesis of imidazo[1,5-*a*]pyrazines **3**. Now we describe herein a novel formation of imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivatives **3**.

The mesoionic oxazoles **1a-h** are easily prepared from *N*-acyl-*N*-alkylglycines **4** in a one step through the cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at C-4 position of an intermediary mesoionic 1,3-oxazolium-5-olates (Scheme 1).[15]

We found that, upon treatment of **1a** with 3 molar equiv. of TosMIC in the presence of DBU and O_2, a clean reaction occurred, leading to the formation of imidazo[1,5-*a*]pyrazin-8(7*H*)-one **3a** in 91% yield. The substituents on C2 and N3 of the mesoionic ring on the reaction were investigated and the results are shown in Table 1. Mesoionics bearing either alkyl or aryl substituents at the N3 position all functioned well, giving imidazo[1,5-*a*]pyrazinones **3** in fair to excellent yields. 2-Arylmesoionic oxazoles **1a**,**b**,**d-j** were easily transformed to the products **3a**,**b**,**d-j** in high yields (entries 1, 2, and 4-10). Unfortunately, 2-methylmesoionic **1c**, bearing α-hydrogens, afforded the **3c** only in 18% yield (entry 3).

Table 1. Imidazo[1,5-*a*]pyrazin-8(7*H*)-ones **3** from mesoionic oxazoles **1**



Entry	**1**	R^1	R^2	Yield (%)
1	**a**	Me	Ph	**3a** (91)
2	**b**	Ph	Ph	**3b** (77)
3	**c**	Ph	Me	**3c** (18)
4	**d**	Me	4-BrC_6H_4	**3d** (79)
5	**e**	Me	4-$MeOC_6H_4$	**3e** (82)
6	**f**	$PhCH_2$	Ph	**3f** (83)
7	**g**	4-$MeOC_6H_4CH_2$	Ph	**3g** (86)
8	**h**	$PhCH_2$	4-$MeOC_6H_4$	**3h** (99)
9	**i**	Ph	4-$NO_2C_6H_4$	**3i** (76)
10	**j**	Ph	4-$MeOC_6H_4$	**3j** (99)

The molecular structure of **3a** was unequivocally confirmed by X-ray diffraction study of single crystals (Figure 2).[16]

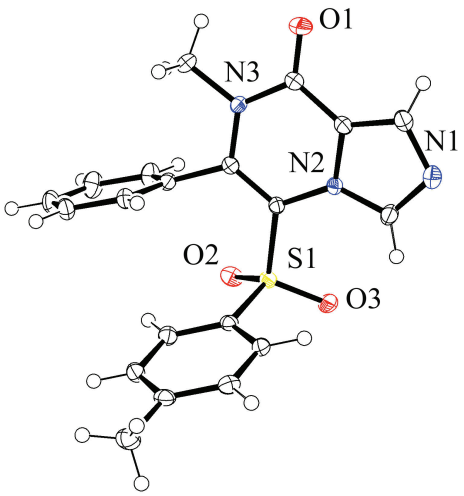


Figure 2. Ortep drawing of **3a** (50% probability)

A tentative mechanism which accounts for the formation of the pyrazin-2(1*H*)-ones (**2**) is described in the communication.[14] Thus, initial nucleophilic attack by the TosMIC anion on C-2 of **1** gave rise to an adduct which is converted to the 2-pyrazinones **2** *via* a ring closure followed by auto-oxidation.[7] The reaction of TosMIC with aldimines to form imidazoles is known as the van Leusen imidazole synthesis.[17] The imidazo[1,5-*a*]pyrazine core was reported to be synthesized *via* condensation with TosMIC with 2-pyrazinone derivative.[11,18] Therefore, the formation of imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivatives (**3**) could be explained by the further reaction of the **2** with second TosMIC. Indeed, the reaction of **2a** with TosMIC gave **3a** in 94% yield (Scheme 1). The C3-position of **2** is elctrophilically reactive position in the pyrazinone core[19] and could undergo nucleophilic attack by nucleophiles such as being part of an imine system.

We described herein a facile synthesis of imidazo[1,5-*a*]pyrazin-8(7*H*)-one derivatives **3** from mesoionic oxazoles **1** in good yields. This unique ring transformation reaction of mesoionic oxazoles with TosMIC was not anticipated but the reaction is general as evidenced by the examples indicated in Table 1. The method appears to be useful and convenient in terms of the ready accessibility of the starting materials, operational simplicity and mild condition. The obtained compounds are of interest for the investigation of the potential biological activity.

EXPERIMENTAL

All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Bruker AVANCE500 spectrometer with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C-NMR spectra were obtained on a Bruker AVANCE500 spectrometer (at 126 MHz). Both ^{1}H- and ^{13}C-NMR spectral data are reported in parts per million (δ) relative to Me_4Si. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer.

Low- and high-resolution MS were obtained with a JEOL JMS-GC mate II spectrometer with a direct inlet system at 70 eV and a Bruker micrOTOF-Q mass spectrometer with methanol as the solvent. Elemental analyses were carried out on a Yanaco CHN Corder MT-5, and X-ray crystallographic data were recorded on a Rigaku VariMax SaturnCCD724/α diffractometer using graphite monochromated Mo-Kα radiation at the Advanced Research Support Center, Ehime University. Standard work-up means that the organic layers were finally dried over Na_2SO_4, filtered, and concentrated *in vacuo* below 37 °C using a rotary evaporator.

Materials: The following compounds were prepared by employing the reported method.

***N*-Benzoyl-*N*-methylglycine (4a):** mp 101−104 °C (mp[20] 102−104 °C).

***N*-Benzoyl-*N*-phenylglycine (4b):** mp 126−128 °C (mp[20] 127−129 °C).

***N*-Acetyl-*N*-phenylglycine (4c):** mp 196−198 °C (mp[21] 193−195 °C).

***N*-(4-Bromobenzoyl)-*N*-methylglycine (4d):** mp 143–145 °C (mp[22] 147–150 °C).

***N*-(4-Methoxybenzoyl)-*N*-methylglycine (4e):** mp 151–154 °C (mp[20] 155–160 °C).

***N*-Benzoyl-*N*-benzylglycine (4f):** mp 103−104 °C (mp[23] 106−107 °C).

***N*-Benzoyl-*N*-(4-methoxyphenylmethyl)glycine (4g):** mp 157−158 °C (mp[24] 157−158 °C).

***N*-Benzyl-*N*-(4-methoxybenzoyl)glycine (4h):** mp 149−151 °C (mp[22] 149−151 °C).

***N*-(4-Nitrobenzoyl)-*N*-phenylglycine (4i):** mp 178–180 °C (mp[20] 172–175 °C).

***N*-(4-Methoxybenzoyl)-*N*-phenylglycine (4j):** mp 135–137 °C (mp[20] 158–163 °C).

General Procedure for Preparation of 4-Trifluoroacetyl-1,3-oxazolium-5-olates 1a-j: To a stirred suspension of *N*-acyl-*N*-alkylglycine (5.2 mmol) in AcOEt (10 mL), TFAA (2.2 mL, 15.6 mmol) was added at 0 °C, and then the solution was stirred at 0 °C for 3 h. To the mixture, hexane was added. The precipitate was collected by filtration, dried, and recrystallized from hexane/AcOEt to give the product **1a-f**.

4-Trifluoroacetyl-3-methyl-2-phenyl-1,3-oxazolium-5-olate (1a): Pale yellow crystals, 95% yield. mp 161−163 °C (mp[25] 162−163 °C).

4-Trifluoroacetyl-2,3-diphenyl-1,3-oxazolium-5-olate (1b): Yellow crystals, 94% yield. mp 194−196 °C (mp[25] 194−196 °C).

4-Trifluoroacetyl-2-methyl-3-phenyl-1,3-oxazolium-5-olate (1c): White crystals, 90% yield. mp 200−203 °C (mp[25] 211−212 °C).

2-(4-Bromophenyl)-4-trifluoroacetyl-3-methyl-1,3-oxazolium-5-olate (1d): White crystals, 90% yield. mp 188–191 °C (mp[22] 188–191 °C).

4-Trifluoroacetyl-2-(4-methoxyphenyl)-3-methyl-1,3-oxazolium-5-olate (1e): Pale yellow crystals, 82% yield. mp 142–143 °C (AcOEt/hexane). IR (KBr) ν_{max} 3027, 2958, 2897, 1789, 1629, 1601, 1513, 1431, 1264, 1185, 1155, 1015, 846, 736 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 3.93 (s, 3H, NC*H*$_3$), 4.12

(s, 3H, OC*H*$_3$), 7.11 (d, *J* = 8.9 Hz, 2H, Ar*H*), 7.73 (d, *J* = 9.0 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 37.5 (N*C*H$_3$), 55.8 (O*C*H$_3$), 97.3 (*C*), 112.2, 115.3, 116.9 (q, $^1J_{C\text{-}F}$ = 288.8 Hz, *C*F$_3$), 131.6, 153.9 (*C*), 157.9 (*C*), 164.2 (*C*), 167.3 (q, $^2J_{C\text{-}F}$ = 37.6 Hz, *C*OCF$_3$) ppm. MS *m/z*: 301 (M^+, 58.8), 135 (100). HRMS (EI) for $C_{13}H_{10}F_3NO_4$ (M^+): Calcd, 301.0562. Found, 301.0547.

3-Benzyl-4-trifluoroacetyl-2-phenyl-1,3-oxazolium-5-olate (1f): White crystals, 83% yield. mp 143−145 °C (mp[24] 143–145 °C).

4-Trifluoroacetyl-3-(4-methoxybenyl)-2-phenyl-1,3-oxazolium-5-olate (1g): White crystals, 75% yield. mp 147–148 °C (mp[24] 147–148 °C).

3-Benzyl-4-trifluoroacetyl-2-(4-methoxyphenyl)-1,3-oxazolium-5-olate (1h): White crystals, 89% yield. mp 158−160 °C (mp[23] 158−160 °C).

4-Trifluoroacetyl-2-(4-nitrophenyl)-3-phenyl-1,3-oxazolium-5-olate (1i): Yellow crystals, 70% yield. mp 175–178 °C (AcOEt/hexane). IR (KBr) ν_{max} 3080, 2917, 2850, 1779, 1645, 1523, 1353, 1261, 1208, 1153, 855, 826, 721 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.64 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.63 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.70 (t, *J* = 7.6 Hz, 1H, Ar*H*), 8.18 (d, *J* = 9.0 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 98.4 (*C*), 116.4 (q, $^1J_{C\text{-}F}$ = 289.1 Hz, *C*F$_3$), 124.2, 126.1, 127.5, 130.5, 130.6, 131.8, 133.8, 149.3 (*C*), 150.0 (*C*), 157.1 (*C*), 166.7 (q, $^2J_{C\text{-}F}$ = 38.4 Hz, *C*OCF$_3$) ppm. MS *m/z*: 378 (M^+, 0.8), 150 (100). HRMS (EI) for $C_{17}H_9F_3N_2O_5$ (M^+): Calcd, 378.0464. Found, 378.0461.

4-Trifluoroacetyl-2-(4-methoxyphenyl)-3-phenyl-1,3-oxazolium-5-olate (1j): Pale yellow crystals, 93% yield. mp 203–205 °C (mp[22] 182–185 °C).

General Procedure for Synthesis of Imidazo[1,5-*a*]pyrazin-8(7*H*)-ones 3a-j: To a stirred solution of TosMIC (293 mg, 1.50 mmol) in DMF (3 mL), DBU (304 mg, 2.00 mmol) was added at 0 °C, and then the mixture was stirred for 1 h under atmosphere of oxygen. To the mixture, 4-trifluoroacetyl-1,3-oxazolium-5-olate **1a-j** (0.50 mmol) was added, and then the whole was stirred at 0 °C for an additional 5 h. After workup with aq. Na_2CO_3, the mixture was extracted with AcOEt (30 mL x 3). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1 to 1:3) to give the product **3a-j**.

7-Methyl-5-[(4-methylphenyl)sulfonyl]-6-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3a): Pale yellow crystals, 91% yield. mp 178–180 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3165, 3055, 2923, 1674, 1663, 1595, 1336, 1321, 1152, 924, 875, 790, 701 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H, ArC*H*$_3$), 2.98 (s, 3H, NC*H*$_3$), 7.21–7.23 (m, 4H, Ar*H*), 7.47 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.50 (t, *J* = 7.3 Hz, 2H, Ar*H*), 7.57 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 8.07 (d, *J* = 0.4 Hz, 1H, *H*-1), 8.96 (d, *J* = 0.5 Hz, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H$_3$), 32.2 (N*C*H$_3$), 117.7 (*C*), 122.4 (*C*), 127.1 (*C*H), 128.7 (*C*H),

129.8 (*C*H), 129.9 (*C*H), 130.4 (*C*H), 131.9 (*C*-1), 134.9 (*C*-3), 137.5 (*C*), 139.5 (*C*-6), 145.5 (*C*), 155.2 (*C*O) ppm. MS *m/z*: 379 (M^+, 100). *Anal.* Calcd for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.21; H, 4.80; N, 11.00.

5-[(4-Methylphenyl)sulfonyl]-6,7-diphenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3b): Pale yellow crystals, 77% yield. mp 263–266 °C (dec.) ($CHCl_3$/hexane). IR (KBr) ν_{max} 3182, 3051, 1692, 1583, 1493, 1433, 1342, 1324, 1267, 1169, 1151, 1086, 991, 817, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H, ArCH_3), 6.91 (d, *J* = 8.1 Hz, 2H, Ar*H*), 6.99 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.10–7.22 (m, 8H, Ar*H*), 7.47 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.13 (s, 1H, *H*-1), 9.08 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.7 (*C*H_3), 118.1, 122.6, 127.3, 127.4, 128.5, 128.8, 129.4, 129.5, 129.8, 129.9, 131.3, 132.9, 135.5, 135.8, 137.5, 139.6, 145.4, 154.9 (*C*O) ppm. MS *m/z*: 441 (M^+, 60.7), 77 (100). HRMS (EI) for $C_{25}H_{19}N_3O_3S$ (M^+): Calcd, 441.1147. Found, 441.1152.

6-Methyl-5-[(4-methylphenyl)sulfonyl]-7-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3c): A yellow solid, 18% yield. mp 232–235 °C (dec.) ($CHCl_3$/hexane). IR (KBr) ν_{max} 3194, 3065, 2927, 1691, 1592, 1492, 1375, 1326, 1161, 1089, 944, 894, 818, 770 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H, ArCH_3), 2.44 (s, 3H, CCH_3), 7.18 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.37 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.48–7.55 (m, 3H, Ar*H*), 7.83 (d, *J* = 8.2 Hz, 2H, Ar*H*), 8.02 (s, 1H, *H*-1), 8.92 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 17.8 (*C*H_3), 21.7 (*C*H_3), 116.8, 122.2, 126.6, 128.8, 129.7, 130.0, 130.4, 132.7, 134.8, 136.1, 137.5, 137.6, 145.8, 154.9 (*C*O) ppm. MS *m/z*: 379 (M^+, 62), 77 (100). HRMS (EI) for $C_{20}H_{17}N_3O_3S$ (M^+): Calcd, 379.0991. Found, 379.0974.

6-(4-Bromophenyl)-7-methyl-5-[(4-methylphenyl)sulfonyl]imidazo[1,5-*a*]pyrazin-8(7*H*)-one (3d): White crystals, 79% yield. mp 180–183 °C (acetone/hexane). IR (KBr) ν_{max} 3185, 2970, 1671, 1598, 1438, 1371, 1338, 1154, 1010, 831, 745 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.41 (s, 3H, ArCH_3), 2.98 (s, 3H, NCH_3), 7.11 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.25 (d, *J* = 8.2 Hz, 2H, Ar*H)*, 7.47 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.64 (d, *J* = 6.8 Hz, 2H, Ar*H*), 8.04 (s, 1H, *H*-1), 8.94 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.7 (*C*H_3), 32.2 (N*C*H_3), 117.9, 122.3, 125.1, 127.0, 128.8, 130.0, 131.4, 132.0, 132.1, 134.9, 137.3, 138.2, 145.7, 155.0 (*C*O) ppm. MS *m/z*: 459 (M^++2, 90.7), 457 (M^+, 86.7), 54 (100). HRMS (EI) for $C_{20}H_{16}BrN_3O_3S$ (M^+): Calcd, 457.0096. Found, 457.0093.

6-(4-Methoxyphenyl)-7-methyl-5-[(4-methylphenyl)sulfonyl]imidazo[1,5-*a*]pyrazin-8(7*H*)-one (3e): Ocher crystals, 82% yield. mp 173–176 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3155, 2966, 2925, 1696, 1609, 1508, 1438, 1318, 1254, 1169, 1152, 1083, 1025, 992, 851, 804 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H, ArCH_3), 2.99 (s, 3H, NCH_3), 3.91 (s, 3H, OCH_3), 6.98 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.10 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.21 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.45 (d, *J* = 8.4 Hz, 2H, Ar*H*), 8.06 (s, 1H, *H*-1), 8.99 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H_3), 32.1 (N*C*H_3), 55.4 (O*C*H_3), 114.1, 118.0, 121.6, 122.5, 127.0, 129.8, 131.3, 131.7, 134.9, 137.7, 139.5, 145.3, 155.3 (*C*O), 161.1 (*C*)

ppm. MS *m/z*: 409 (M^+, 100). HRMS (EI) for $C_{21}H_{19}N_3O_4S$ (M^+): Calcd, 409.1096. Found, 409.1077.

7-Benzyl-5-[(4-methylphenyl)sulfonyl]-6-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3f): Pale yellow crystals, 83% yield. mp 232–235 °C (dec.) ($CHCl_3$/hexane). IR (KBr) ν_{max} 3158, 3059, 3026, 1676, 1596, 1446, 1359, 1340, 1258, 1162, 1087, 885, 810, 789 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H, ArC*H*$_3$), 4.85 (s, 2H, NC*H*$_2$Ar), 6.71 (d, *J* = 6.8 Hz, 2H, Ar*H*), 6.95 (d, *J* = 7.1 Hz, 2H, Ar*H*), 7.14–7.21 (m, 5H, Ar*H*), 7.29 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.43 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.48 (t, *J* = 7.6 Hz, 1H, Ar*H*), 8.14 (s, 1H, *H*-1), 9.00 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H$_3$), 47.3 (N*C*H$_2$), 118.3, 122.5, 126.8, 127.1, 127.5, 127.9, 128.4, 128.7, 129.9, 130.3, 130.6, 132.6, 135.2, 136.2, 137.4, 139.4, 145.5, 155.3 (*C*O) ppm. MS *m/z*: 455 (M^+, 41.6), 91 (100). HRMS (EI) for $C_{26}H_{21}N_3O_3S$ (M^+): Calcd, 455.1304. Found, 455.1319.

7-(4-Methoxyphenylmethyl)-5-[(4-methylphenyl)sulfonyl]-6-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3g): Pale yellow crystals, 86% yield. mp 183–185 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3144, 3051, 2968, 1676, 1591, 1511, 1440, 1354, 1340, 1252, 1162, 1086, 1031, 921, 810, 786 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H, ArC*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 4.78 (s, 2H, NC*H*$_2$Ar), 6.64 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.68 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.97 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.20 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.33 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.42 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.50 (t, *J* = 7.6 Hz, 1H, Ar*H*), 8.12 (s, 1H, *H*-1), 8.99 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H$_3$), 46.8 (N*C*H$_2$), 55.2 (O*C*H$_3$), 113.7, 118.1, 122.5, 127.1, 127.9, 128.3, 128.5, 128.8, 129.9, 130.3, 130.7, 132.5, 135.1, 137.5, 139.4, 145.4, 155.4 (*C*O), 159.0 (*C*) ppm. MS *m/z*: 485 (M^+, 35.6), 121 (100). HRMS (EI) for $C_{27}H_{23}N_3O_4S$ (M^+): Calcd, 485.1409. Found, 485.1419.

7-Benzyl-6-(4-methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]imidazo[1,5-*a*]pyrazin-8(7*H*)-one (3h): A pale yellow oil, 99% yield. IR (neat) ν_{max} 3174, 3031, 2959, 1683, 1609, 1539, 1508, 1437, 1357, 1295, 1252, 1157, 1087, 1027, 927, 835, 749 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.39 (s, 3H, ArC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 4.86 (s, 2H, NC*H*$_2$Ar), 6.75 (d, *J* = 7.1 Hz, 2H, Ar*H*), 6.78 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.14–7.20 (m, 5H, Ar*H*), 7.42 (d, *J* = 8.3 Hz, 2H, Ar*H*), 8.12 (s, 1H, *H*-1), 9.02 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H$_3$), 47.2 (N*C*H$_2$), 55.4 (O*C*H$_3$), 113.4, 118.6, 120.6, 122.5, 126.8, 127.1, 127.5, 128.4, 129.8, 132.1, 132.4, 135.2, 136.3, 137.6, 139.4, 145.3, 155.4 (*C*O), 161.0 (*C*) ppm. MS *m/z*: 485 (M^+, 77.8), 91 (100). HRMS (EI) for $C_{27}H_{23}N_3O_4S$ (M^+): Calcd, 485.1409. Found, 485.1419.

6-(4-Nitrophenyl)-5-[(4-methylphenyl)sulfonyl]-7-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3i): Yellow crystals, 76% yield. mp 244–245 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3181, 3006, 2980, 1684, 1587, 1531, 1492, 1341, 1324, 1153, 1084, 866, 815, 747 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.43 (s, 3H, ArC*H*$_3$), 6.94 (dd, *J* = 8.0, 2.1 Hz, 2H, Ar*H*), 7.16–7.22 (m, 3H, Ar*H*), 7.28 (t, *J* = 8.3 Hz, 4H, Ar*H*),

7.53 (d, *J* = 8.4 Hz, 2H, Ar*H*), 8.00 (d, *J* = 8.7 Hz, 2H, Ar*H*), 8.10 (s, 1H, *H*-1), 8.98 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.7 (*C*H_3), 118.0, 122.3, 122.5, 127.2, 129.2, 129.3, 129.7, 130.3, 132.3, 133.3, 135.4, 136.2, 136.9, 137.1, 140.4, 146.3, 148.0, 154.5 (*C*O) ppm. MS *m/z*: 486 (M^+, 66.9), 77 (100). HRMS (EI) for $C_{25}H_{18}N_4O_5S$ (M^+): Calcd, 486.0998. Found, 486.1024.

6-(4-Methoxyphenyl)-5-[(4-methylphenyl)sulfonyl]-7-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3j): Pale yellow crystals, 99% yield. mp 253–256 °C (dec.) ($CHCl_3$/hexane). IR (KBr) ν_{max} 3155, 2966, 2925, 1695, 1609, 1508, 1438, 1317, 1254, 1169, 1152, 1083, 851, 804, 708 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.40 (s, 3H, ArC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 6.60 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.85–6.91 (m, 4H, Ar*H*), 7.13–7.21 (m, 5H, Ar*H*), 7.45 (d, *J* = 8.4 Hz, 2H, Ar*H*), 8.12 (s, 1H, *H*-1), 9.09 (s, 1H, *H*-3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 21.6 (*C*H_3), 55.2 (O*C*H_3), 112.9, 118.4, 121.2, 122.8, 127.2, 128.4, 128.8, 129.7, 129.8, 132.8, 132.8, 135.5, 136.0, 137.7, 139.6, 145.3, 155.0 (*C*O), 160.3 (*C*) ppm. MS *m/z*: 471 (M^+, 100). HRMS (EI) for $C_{26}H_{21}N_3O_4S$ (M^+): Calcd, 471.1253. Found, 471.1255.

Conversion of 1-Methyl-5-[(4-methylphenyl)sulfonyl]-6-phenylpyrazin-2(1*H*)-one (2a) to 7-Methyl-5-[(4-methylphenyl)sulfonyl]-6-phenylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (3a): To a stirred solution of TosMIC (43 mg, 0.220 mmol) in DMF (1 mL), DBU (46 mg, 0.294 mmol) was added at 0 °C, and then the mixture was stirred for 30 min under atmosphere of argon. To the mixture, **2a** (50 mg, 0.147 mmol) was added, and then the whole was stirred at rt for an additional 2 h. After workup with aq. Na_2CO_3, the mixture was extracted with AcOEt (30 mL x 3). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 1:1 to 1:2) to give the product **3a** (52 mg, 94% yield).

Crystal Data Refinements Details

Data Collection: A colorless prism crystal of $C_{20}H_{17}N_3O_3S$ (**3a**; CCDC no. 1047969) having approximate dimensions of 0.200 x 0.160 x 0.100 mm was mounted on a glass fiber. All measurements were made on an Rigaku Saturn 724 diffractometer using multi-layer mirror monochromated Mo-Kα radiation. The crystal-to-detector distance was 45.00 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions: a = 11.948(2) Å, b = 31.727(5) Å, c = 9.897(2) Å, β = 97.513(2)°, V = 3719.5(10) Å^3. For Z = 8 and F.W. = 379.43, the calculated density is 1.355 g/cm^3. The reflection conditions of: h0l: l = 2n, 0k0: k = 2n, uniquely determine the space group to be: $P2_1/n$ (#14).

The data were collected at a temperature of −172 ± 1 °C to a maximum 2θ value of 62.9°. A total of 1440 oscillation images were collected. A sweep of data was done using ω oscillations from −110.0 to 70.0° in 0.5° steps. The exposure rate was 2.0 [sec./°]. The detector swing angle was −19.97°. A second sweep was performed using ω oscillations from −110.0 to 70.0° in 0.5° steps. The exposure rate was 2.0 [sec./°]. The detector swing angle was −19.97°. Another sweep was performed using ω

oscillations from −110.0 to 70.0° in 0.5° steps. The exposure rate was 2.0 [sec./°]. The detector swing angle was −19.97°. Another sweep was performed using ω oscillations from −110.0 to 70.0° in 0.5° steps. The exposure rate was 2.0 [sec./°]. The detector swing angle was −19.97°. The crystal-to-detector distance was 45.00 mm. Readout was performed in the 0.141 mm pixel mode.

Data Reduction: Of the 60923 reflections that were collected, 8539 were unique (R_{int} = 0.0445). Data were collected and processed using CrystalClear (Rigaku).[26]

The linear absorption coefficient, μ, for Mo-Kα radiation is 1.997 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.892 to 0.980. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods[27] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[28] on F^2 was based on 8539 observed reflections and 491 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: $R1 = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.0400$, $wR2 = [\Sigma (w (Fo^2 - Fc^2)^2)/ \Sigma w(Fo^2)^2]^{1/2} = 0.0981$.

The standard deviation of an observation of unit weight[29] was 1.05. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.34 and −0.50 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[30] Anomalous dispersion effects were included in Fcalc;[31] the values for Δf' and Δf'' were those of Creagh and McAuley.[32] The values for the mass attenuation coefficients are those of Creagh and Hubbell.[33] All calculations were performed using the CrystalStructure[34] crystallographic software package except for refinement, which was performed using SHELXL-97.[35]

REFERENCES

1. (a) J.-X. Wang, J. A. McCubbin, M. Jin, R. S. Laufer, Y. Mao, A. P. Crew, M. J. Mulvihill, and V. Snieckus, *Org. Lett.*, 2008, **10**, 2923; (b) J. Board, J.-X. Wang, A. P. Crew, M. Jin, K. Foreman, M. J. Mulvihill, and V. Snieckus, *Org. Lett.*, 2009, **11**, 5118; (c) A. Shaabani, A. Maleki, and H. Mofakham, *Mol. Divers.*, 2009, **13**, 63.
2. R. Goel, V. Luxami, and K. Paul, *Org. Biomol. Chem.*, 2015, **13**, 3525.
3. A. Gopalsamy and M. Shi, *Org. Lett.*, 2003, **5**, 3907; (b) O. A. Attanasi, G. Favi, G. Giorgi, R. Majer, F. R. Perrulli, and S. Santeusanio, *Org. Biomol. Chem.*, 2014, **12**, 4610.
4. M. Jin, A. Kleinberg, A. Cooke, P. C. Gokhale, K. Foreman, H. Dong, K. W. Siu, M. A. Bittner, K. M. Mulvihill, Y. Yao, D. Landfair, M. O'Connor, G. Mak, J. A. Pachter, R. Wild, M.

Rosenfeld-Franklin, Q. Ji, and M. J. Mulvihill, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1176.

5. A. P. Crew, S. V. Bhagwat, H. Dong, M. A. Bittner, A. Chan, X. Chen, H. Coate, A. Cooke, P. C. Gokhale, A. Honda, M. Jin, J. Kahler, C. Mantis, M. J. Mulvihill, P. A. Tavares-Greco, B. Volk, J. Wang, D. S. Werner, L. D. Arnold, J. A. Pachter, R. Wild, and N. W. Gibson, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2092.
6. M. Jin, J. Wang, A. Kleinberg, M. Kadalbajoo, K. W. Siu, A. Cooke, M. A. Bittner, Y. Yao, A. Thelemann, Q. Ji, S. Bhagwat, K. M. Mulvihill, J. A. Rechka, J. A. Pachter, A. P. Crew, D. Epstein, and M. J. Mulvihill, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 979.
7. K. D. Robarge, W. Lee, C. Eigenbrot, M. Ultsch, C. Wiesmann, R. Heald, S. Price, J. Hewitt, P. Jackson, P. Savy, B. Burton, E. F. Choo, J. Pang, J. Boggs, A. Yang, X. Yang, and M. Baumgardner, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4714.
8. J. Liu, D. Guiadeen, A. Krikorian, X. Gao, J. Wang, S. B. Boga, A.-B. Alhassan, Y. Yu, H. Vaccaro, S. Liu, C. Yang, H. Wu, A. Cooper, J. de Man, A. Kaptein, K. Maloney, V. Hornak, Y.-D. Gao, T. O. Fischmann, H. Raaijmakers, D. Vu-Pham, J. Presland, M. Mansueto, Z. Xu, E. Leccese, J. Zhang-Hoover, I. Knemeyer, C. G. Garlisi, N. Bays, P. Stivers, P. H. Brandish, A. Hicks, R. Kim, and J. A. Kozlowski, *ACS Med. Chem. Lett.*, 2016, **7**, 198.
9. R. A. Hartz, P. J. Gilligan, K. K. Nanda, A. J. Tebben, L. W. Fitzgerald, and K. Miller, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 291.
10. O. Kinzel, A. Alfieri, S. Altamura, M. Brunetti, S. Bufali, F. Colaceci, F. Ferrigno, G. Filocamo, M. Fonsi, P. Gallinari, S. Malancona, J. I. M. Hernando, E. Monteagudo, M. V. Orsale, M. C. Palumbi, V. Pucci, M. Rowley, R. Sasso, R. Scarpelli, C. Steinkuhler, and P. Jones, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4429.
11. H. Mukaiyama, T. Nishimura, S. Kobayashi, T. Ozawa, N. Kamada, Y. Komatsu, S. Kikuchi, H. Oonota, and H. Kusama, *Bioorg. Med. Chem.*, 2007, **15**, 868.
12. (a) E. Abushanab, A. P. Bindra, L. Goodman, and H. Peterson, Jr., *J. Org. Chem.*, 1973, **38**, 2049; (b) V. A. Mamedov, A. A. Kalinin, N. A. Zhukova, V. V. Syakaev, I. Kh. Rizvanov, S. K. Latypov, and O. G. Sinyashin, *Tetrahedron*, 2015, **71**, 147.
13. (a) T. Trcek, A. Meden, and B. Vercek, *Synlett*, 2000, **10**, 1458; (b) A. Gopalsamy and M. Shi, *Org. Lett.*, 2003, **5**, 3907.
14. R. Saijo, K. Kurihara, K. Akira, H. Uno, and M. Kawase, *Tetrahedron Lett.*, 2013, **54**, 4418.
15. R. Saijo, H. Uno, S. Mori, and M. Kawase, *Chem. Commun.*, 2016, **52**, 8006.
16. The structure of **3a** was confirmed by X-ray analysis (CCDC 1047969).
17. S. P. J. M. van Nispen, C. Mensink, and A. M. van Leusen, *Tetrahedron Lett.*, 1980, **21**, 3723.
18. P. Chen, J. C. Barrish, E. Iwanowicz, J. Lin, M. S. Bedbarz, and B.-C. Chen, *Tetrahedron Lett.*,

2001, **42**, 4293.

19. (a) S. V. Pawar, V. G. Pawar, W. Dehaen, and W. M. De Borggraeve, *Org. Lett.*, 2008, **10**, 4473; (b) V. P. Mehta, A. K. Sharma, S. G. Modha, S. Sharma, T. Meganathan, V. S. Parmar, and E. Van der Eycken, *J. Org. Chem.*, 2011, **76**, 2920; (c) N. M. Mishra, V. A. Peshkov, O. P. Pereshivko, S. G. Modha, and E. Van der Eycken, *Tetrahedron Lett.*, 2012, **53**, 4676.
20. J. Deruiter, B. E. Swearingen, V. Wandreker, and C. A. Mayfield, *J. Med. Chem.*, 1991, **34**, 2120.
21. J. DeRuiter, B. E. Swearingen,V. Wandrekar, and C. A. Mayfield, *J. Med. Chem.*, 1989, **32**, 1033.
22. M. Kawase and H. Koiwai, *Chem. Pharm. Bull.*, 2008, **56**, 433.
23. M. Kawase, S. Saito, and T. Kurihara, *Chem. Pharm. Bull.*, 2001, **49**, 461.
24. R. Saijo, Y. Hagimoto, and M. Kawase, *Org. Lett.*, 2010, **12**, 4776.
25. C. V. Greco, R. P. Gray, and V. G. Grosso, *J. Org. Chem.*, 1967, **32**, 4101.
26. CrystalClear: Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, (c) 2000. J. W. Pflugrath, *Acta Crystallogr*., 1999, **D55**, 1718.
27. SIR2004: M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, and R. Spagna, 2005.
28. Least Squares function minimized (SHELXL97): $\Sigma w(F_o^2-F_c^2)^2$ where w = Least Squares weights.
29. Standard deviation of an observation of unit weight: $[\Sigma w(F_o^2-F_c^2)^2/(N_o-N_v)]^{1/2}$ where: N_o = number of observations, N_v = number of variables.
30. D. T. Cromer and J. T. Waber, in *International Tables for X-ray Crystallography*, The Kynoch Press, Birmingham, England, 1974, vol. IV, Table 2.2 A.
31. J. A. Ibers and W. C. Hamilton, *Acta Crystallogr.*, 1964, **17**, 781.
32. D. C. Creagh and W. J. McAuley, in *International Tables for Crystallography*, ed. by A. J. C. Wilson, Kluwer, Academic Publishers, Boston, 1992, vol. C, pp. 219–222, Table 4.2.6.8.
33. D. C. Creagh and J. H. Hubbell, in *International Tables for Crystallography*, ed. by A. J. C. Wilson, Kluwer, Academic Publishers, Boston, 1992, vol. C, pp. 200–206, Table 4.2.4.3.
34. CrystalStructure 4.0: Crystal Structure Analysis Package, Rigaku Corporation (2000–2010), Tokyo 196-8666, Japan.
35. SHELX97: G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.