2-Protecting Groups for 5-Lithiation in the Syntheses of Imidazoles

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Various substituents have been examined as possible 2-protecting groups against organolithium reagents in the syntheses of imidazoles on the basis of the ease of decarboxylation of imidazole-2-carboxylic acids and cleavage of the C(2)–Si bond. The tertiary amido function and t-butyldimethylsilyl (TBDMS) group at the 2-position permit quantitative 5-lithiation of *N*-substituted imidazoles. Deprotection of the amido function occurs under alkaline conditions while the TBDMS group is removed by several reagents. The TBDMS substituent is stable to butyl-lithium at temperatures up to −10 °C.

Although several reports have been made with regard to protection of the 1-position of imidazoles in reactions involving organometallic reagents,[1] only a few examples of 2-protecting groups exist. The phenylthio group, introduced more than a decade ago by Breslow's team,[2] appears to be the only example of a 2-protecting group that survives normal work-up procedures. It is removed by treatment with aluminium amalgam. Use of trimethylsilyl (TMS) and triethylsilyl (TES) groups has been limited to *in situ* 2-protection owing to their ease of desilylation.[3–5] Halogen–metal exchange reactions have been employed in the preparation of 5-lithio intermediates.[6] The procedure involves syntheses of neurotoxic 2,4,5-trihalogenated intermediates which are later subjected to sequential exchange reactions in the order 2→5→4. Invariably, the product obtained by this methodology is the 4-halogeno derivative of the 1,5-disubstituted target molecule. The procedure is, thus, limited in scope and inconvenient.

As part of a continuing interest in the metallation of imidazoles [3,7] 2-substituents that are stable enough to act as protecting groups against organolithium reagents were investigated.

Results and Discussion

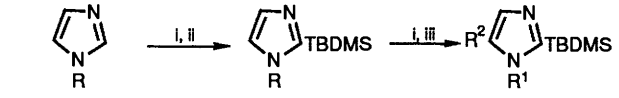
The TBDMS substituent was introduced by treatment of *N*-substituted 2-lithio imidazoles with t-butyldimethylsilyl chloride. The extent of 5-lithiation of the 2-protected imidazoles varied with the nature of the *N*-substituent. Quantitative 5-lithiation of (**3**) was observed in 30 min at −78 °C whereas a yield of 86% was obtained in compound (**4**) under the same reaction conditions. There was no substantial change in yield when the reaction was left at −78 °C for 90 min. Quantitative 5-metallation was achieved, however, when the mixture of (**4**) and butyl-lithium was allowed to warm to −10 °C over 20 min. In both substrates quantitative 5-lithiation was achieved with 1.1 mol equivalent of the base, followed by reaction with various electrophiles to give compounds (**5**)–(**11**) (Scheme 1).

The C(2)–Si bond can be readily cleaved with a range of reagents,[8] some of which were explored for (**3**) in the present study (Table). Some of the reported conditions for desilylation were modified and applied to the syntheses of (**12**) and (**13**) with respect to use of aqueous hydrogen chloride and acetic acid solutions, respectively. In the desilylation of (**3**) with tetrabutylammonium fluoride the substrate (0.9 mmol) in tetrahydrofuran (THF) (2 ml) was stirred with the reagent (2.2 mmol) for 30 min at room temperature. Work-up involved addition of water and extraction with dichloromethane.

Table. Extent of C(2)–Si bond cleavage in compound (**3**) (%).

	Reaction time (h)				
Reagent	0.5	2.5	3.0	3.5	15.0
Bu_4NF	100				
HCl[a]	88	100			
AcOH[b]			100		
NBS					100
CsF		44			100
$BF_3{\cdot}Et_2O$				0.0	6

[a] 2M Aqueous solution. [b] 2:1 Mixture of AcOH–H_2O



(**1**) R = SO_2NMe_2
(**2**) R = CH_2OMe
(**3**) R = SO_2NMe_2
(**4**) R = CH_2OMe
(**5**) R^1 = SO_2NMe_2, R^2 = D
(**6**) R^1 = SO_2NMe_2, R^2 = $C(OH)Ph_2$
(**7**) R^1 = SO_2NMe_2, R^2 = Me
(**8**) R^1 = SO_2NMe_2, R^2 = Cl
(**9**) R^1 = SO_2NMe_2, R^2 = CH(OH)Ph
(**10**) R^1 = CH_2OMe, R^2 = D
(**11**) R^1 = CH_2OMe, R^2 = $C(OH)Ph_2$

Scheme 1. *Reagents:* i, BuLi; ii, TBDMS-Cl; iii, E^+.

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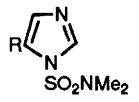
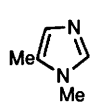


(12) R = C(OH)Ph$_2$
(13) R = Me



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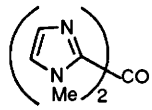
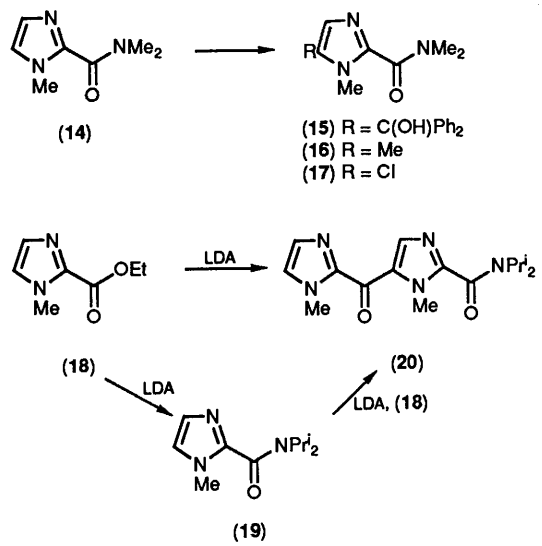


(22)

Separation of water-insoluble silyl residues from (1) in the use of tetrabutylammonium fluoride, aqueous hydrogen chloride and acetic acid solutions was achieved by decantation prior to solvent extraction. Use of *N*-bromosuccinimide (NBS), cesium fluoride, and boron trifluoride–diethyl ether complex followed reported procedures.[8]

It has been reported that *N*-deprotection is also observed with 2-deprotection in the syntheses of the 5-chloro and 5-hydroxymethyl derivatives of TES-protected imidazoles.[4] The TBDMS protecting group appears suitable in syntheses that require further manipulation of the imidazole nucleus *via* lithiation reactions since the 5-chloro and 5-hydroxymethyl derivatives (6), (8), (9), and (11) are isolable (Scheme 1). Subsequent desilylation could be made a function of the nature of the substrate in view of the range of reagents available for C–Si bond cleavage.

The carboxamide (14) undergoes nucleophilic attack with butyl-lithium at −78 °C. Quantitative 5-lithiation is observed, however, with lithium di-isopropylamide (LDA) in 25 min at −78 °C. Work-up with various electrophiles gave (15)–(17). An attempted metallation of the carboxylate (18) with LDA at



(14)

(15) R = C(OH)Ph$_2$
(16) R = Me
(17) R = Cl

(18)

(19)

(20)

Scheme 2.

−78 °C gave what was identified as (20). This probably arises by nucleophilic attack by LDA on (18) to give (19), followed by 5-lithiation of the 2-carboxamide, then attack of the 5-lithio intermediate on another molecule of (18) (Scheme 2). These reactions of (14) and (19) suggest that 5-lithiation with LDA of *N*-substituted imidazoles which possess a tertiary amido function at the 2-position is general. Deprotection occurs under alkaline conditions.[9] 1,5-Dimethylimidazole (21) was isolated in low yield from (16) by routine extraction owing to its solubility in water. The methodology is limited, however, to 5-substituents that are stable to the deprotection conditions.

The cleavage of non-enolisable ketones with a 10:3 mixture of potassium t-butoxide–water in aprotic solvents is reported to yield carboxylic acids.[10] It was thus expected that lithiation at the 5-position of the ketone, (22), followed by work-up with suitable electrophiles, then cleavage, would lead to 1,5-disubstituted derivatives. The carbonyl group was rather attacked by butyl-lithium and LDA at −78 °C. 5-Lithiation probably requires a more sterically hindered base than LDA.

2-Methylimidazoles may be oxidised to give 2-carboxylic acids.[11] Use of the 2-methyl substituent as a 2-protecting group was, therefore, examined. 1,2-Dimethylimidazole is lithiated at the 5-position and on the 2-methyl group under varying conditions.[12] In the present study lithiation with LDA at −78 °C followed by work-up with deuterium oxide and NMR analysis showed deuteriation to the extent of 84% at the 2-methyl group and 18% at the 5-position. These observations limit the synthetic application of the methyl group as a protecting group for the 2-position.

Experimental

General procedures for instrumentation, characterisation, solvent preparation, and analysis have been described earlier.[3,7] Syntheses of compounds (1), (2), and (18) followed reported procedures.[2,3,13] The molecular ion was generated in the mass spectrometer by electron impact except where indicated by CI (chemical impact) for compounds with the thermally labile 2-silyl substituent. ^{1}H NMR spectra were recorded on a Perkin-Elmer R34 (220 MHz) spectrometer in deuteriochloroform with tetramethylsilane as internal lock standard.

2-(*t-Butyldimethylsilyl*)-N,N-*dimethylimidazole*-1-*sulphonamide* (3).—To the sulphonamide (1) (5.30 g, 30.3 mmol) in THF (180 ml) at −78 °C was added butyl-lithium in hexane (32.5 mmol). The mixture was stirred at −78 °C for 15 min and t-butyldimethylsilyl chloride (38.2 mmol) in THF (15 ml) was added. Stirring was continued at room temperature for 1 h and the mixture was then poured into water (20 ml). The organic layer was separated, dried ($MgSO_4$), and solvent evaporated to give an oily solid whose NMR spectrum showed quantitative silylation by inspection of the aromatic region. Chromatography on silica gel with 20% ethyl acetate–light petroleum (b.p. 40–60 °C) as eluant gave the 2-silyl product (3) (7.93 g, 90%), m.p. 63–66 °C; δ_H 0.43 (6 H, s, $SiMe_2$), 1.00 (9 H, s, CMe_3), 2.90 (6 H, s, NMe_2), 7.28 (1 H, d, *J* 1.2 Hz, imidazole 5-H), and 7.37 (1 H, d, *J* 1.2 Hz, imidazole 4-H); *m/z* (CI/NH_3) 290.1357 (M^+ + H, 100%; $C_{11}H_{24}N_3O_2SSi$ requires 290.1358).

2-(*t-Butyldimethylsilyl*)-5-*hydroxydiphenylmethyl*-N,N-*dimethylimidazole*-1-*sulphonamide* (6).—Butyl-lithium in hexane (6.3 mmol) was added to compound (1) (1.03 g, 5.7 mmol) in THF (30 ml) at −78 °C and the mixture stirred for 15 min. t-Butyldimethylsilyl chloride (6.6 mmol) in THF (5 ml) was added and the stirring continued at room temperature for 2 h. The mixture was cooled to −78 °C, butyl-lithium in hexane (6.9 mmol) added, and the stirring continued at −78 °C for 30 min. A portion (1 ml) was quenched with deuterium oxide. Analysis by NMR of the product showed formation of compound (5) to an extent of 100% δ_H 0.41 (6 H, s, $SiMe_2$), 0.98 (9 H, s, CMe_3), 2.88 (6 H, s, NMe_2), and 7.27 (1 H, s, imidazole 4-H).

To the 5-lithio-2-silyl derivative at −78 °C was added

benzophenone (7.5 mmol) in THF (3 ml). The mixture was stirred at room temperature for 2 h and poured into water (20 ml). The aqueous layer was separated and extracted with dichloromethane (10 ml × 4). The extracts and organic layer were combined and the solution was dried ($MgSO_4$) and concentrated. Chromatography on neutral alumina with cyclohexane as eluant gave the *methanol* (**6**) (2.29 g, 86%), m.p. 117–119 °C (from diethyl ether) (Found: C, 61.25; H, 7.1; N, 8.9. $C_{24}H_{33}N_3O_3SSi$ requires C, 61.10; H, 7.07; N, 8.91%); δ_H 0.40 (6 H, s, $SiMe_2$) 1.00 (9 H, s, CMe_3), 6.32 (1 H, s, imidazole 4-H), and 7.28–7.38 (10 H, m, Ph_2); *m/z* (CI/NH_3) 472 (M^+ + H, 100%).

2-(*t-Butyldimethylsilyl*)-5-*methyl*-N,N-*dimethylimidazole*-1-*sulphonamide* (**7**).—The 5-lithio derivative of (**3**) was generated as in the preparation of (**6**) (5.7 mmol), followed by addition of iodomethane (16.1 mmol). The mixture was allowed to warm to room temperature and then poured into water (20 ml). Extraction of the aqueous layer with dichloromethane (10 ml × 2) gave the crude product * as an oil (1.91 g) which was used without further purification: δ_H 0.40 (6 H, s, $SiMe_2$), 1.00 (9 H, s, CMe_3), 2.37 (3 H, s, 5-Me), 2.87 (6 H, s, NMe_2), and 6.93 (1 H, s, imidazole 4-H).

2-(*t-Butyldimethylsilyl*)-5-*chloro*-N,N-*dimethylimidazole*-1-*sulphonamide* (**8**).—*N,N*-Dimethylsulphamoyl chloride (9.3 mmol) was added to the 5-lithio derivative of (**3**) (5.0 mmol) at −78 °C and the mixture stirred at room temperature for 30 min, poured into water (20 ml), and made basic with solid sodium hydrogen carbonate. Extraction of the aqueous layer with dichloromethane (20 ml × 3) and chromatography on silica gel with 10% ethyl acetate–light petroleum (b.p. 40–60 °C) as eluant gave (**8**) (1.38 g, 86%), m.p. 104–107 °C; δ_H 0.38 (6 H, s, $SiMe_2$), 1.00 (9 H, s, CMe_3), 3.00 (6 H, s, NMe_2), and 7.10 (1 H, s, imidazole 4-H); *m/z* (CI/NH_3) 210 [(M^+ + H) − $C_6H_{14}Si$, 27%] † and 46 (100).

5-*Hydroxydiphenylmethyl*-N,N-*dimethylimidazole*-1-*sulphonamide* (**12**).—Benzaldehyde (39.4 mmol) was added to the 5-lithio derivative of (**3**) (24.1 mmol) at −78 °C. The mixture was stirred at room temperature for 30 min and the resulting solution containing (**9**) was carefully poured into 2M aqueous hydrogen chloride (30 ml). The organic layer was separated and extracted with 2M aqueous hydrogen chloride (40 ml × 4). The combined acidic solutions were stirred at room temperature for 30 min, washed with diethyl ether (80 ml × 3), and brought to pH 7 with 50% aqueous sodium hydroxide. The resulting precipitate was extracted with dichloromethane (30 ml × 5) to yield (**12**) (4.48 g, 66%), m.p. 131–134 °C [from ethyl acetate–light petroleum (b.p. 40–60 °C)]; δ_H 2.93 (6 H, s, NMe_2), 6.17 (1 H, s, CH), 6.66 (1 H, s, imidazole 4-H), 7.40–7.53 (5 H, m, Ph), and 7.94 (1 H, s, imidazole 2-H); *m/z* (FAB in glycerol) 282 (M^+ + H, 100%).

2-(*t-Butyldimethylsilyl*)-5-*hydroxydiphenylmethyl*-1-*methoxymethylimidazole* (**11**).—To compound (**2**) (1.33 g, 11.9 mmol) in THF (20 ml) at −78 °C was added butyl-lithium in hexane (12.8 mmol). The mixture was stirred at −78 °C for 30 min, t-butyldimethylsilyl chloride (13.5 mmol) in THF added, and the stirring continued at room temperature for 30 min. A portion of the mixture (2 ml) was removed and quenched with water. Analysis of the resulting product by NMR indicated formation of compound (**4**) to an extent of 94%; δ_H 0.40 (6 H, s, $SiMe_2$), 0.94 (9 H, s, CMe_3), 3.30 (3 H, s, OMe), 5.30 (2 H, s, NCH_2), 7.16 (1 H, d, *J* 1.1 Hz, imidazole 5-H), and 7.27 (1 H, d, *J* 1.1 Hz, imidazole 4-H).

The solution of the 2-silyl derivative was cooled to −78 °C and butyl-lithium in hexane (13.5 mmol) added. The mixture was allowed to warm to −10 °C over 20 min and a portion (1 ml) was removed and treated with deuterium oxide to give compound (**10**), formation of which was found to be 100% by NMR analysis: δ_H 0.40 (6 H, s, $SiMe_2$), 0.94 (9 H, s, CMe_3), 3.30 (3 H, s, OMe), 5.29 (2 H, s, NCH_2), and 7.25 (1 H, s, imidazole 4-H).

The 5-lithio-2-silyl derivative was cooled to −78 °C and benzophenone (14.4 mmol) added. After 1 h at room temperature the mixture was carefully poured into 2M aqueous hydrogen chloride (15 ml). The aqueous layer was separated and extracted with THF (15 ml). The combined organic solutions were concentrated and the residue dissolved in ethyl acetate and the solution dried ($MgSO_4$) and evaporated to give a waxy solid which was not purified further. Analysis by NMR indicated formation of compound (**11**) to an extent of 90%: δ_H 0.53 (6 H, s, $SiMe_2$), 0.93 (9 H, s, CMe_3), 2.98 (3 H, s, OMe), 5.28 (2 H, s, NCH_2), 6.72 (1 H, s, imidazole 4-H), and 7.27–7.44 (10 H, m, Ph_2).

5-*Methyl*-N,N-*dimethylimidazole*-1-*sulphonamide* (**13**).—To the silyl derivative (**7**) (0.10 g, 0.3 mmol) was added acetic acid–water (2:1 mixture; 2 ml). The solution was stirred for 2 h at room temperature, poured into water (2 ml), and neutralised with solid sodium hydrogen carbonate, followed by decantation of the solution from the silyl residue. The aqueous solution was extracted with dichloromethane (2 ml × 3). Analysis of the resulting product by NMR showed formation of (**13**) to an extent of 100%: δ_H 2.40 (3 H, s, Me), 2.90 (6 H, s, NMe_2), 6.84 (1 H, s, imidazole 4-H), and 7.89 (1 H, s, imidazole 2-H).

1-*Methyl*-N,N-*dimethylimidazole*-2-*carboxamide* (**14**).—The 2-lithio derivative of 1-methylimidazole (62.7 mmol) in THF (35 ml) at −78 °C was added to a solution of dimethylcarbamoyl chloride (86.9 mmol) in diethyl ether (20 ml) at −78 °C. Stirring was continued for 2.4 h at −78 °C and 25 min in an ice-bath, and the mixture poured into water (30 ml). The aqueous layer was separated, saturated with sodium chloride, and extracted with trichloromethane (50 ml × 4) to give the ketone (**22**) (15%) and the *carboxamide* (**14**) (8.13 g, 85%), b.p. 96 °C/0.4 mmHg (Found: C, 55.0; H, 7.2; N, 27.2. $C_7H_{11}N_3O$ requires C, 54.88; H, 7.24; N, 27.43%): δ_H 3.10 (3 H, s, CONMe), 3.39 (3 H, s, CONMe), 3.87 (3 H, s, NMe), 6.94 (1 H, d, *J* 1.1 Hz, imidazole 5-H), and 7.05 (1 H, d, *J* 1.1 Hz, imidazole 4-H); *m/z* 153 (M^+, 61%) and 72 (100).

5-*Hydroxydiphenylmethyl*-1-*methyl*-N,N-*dimethylimidazole*-2-*carboxamide* (**15**).—The carboxamide (**14**) (0.51 g, 3.3 mmol) in THF (5.5 ml) was metallated with LDA (4.7 mmol) in THF (2 ml) over 25 min at −78 °C, followed by reaction with benzophenone (6.0 mmol) in THF (5 ml). Work-up of the product of reaction and recrystallisation from ethyl acetate gave (**15**) (1.02 g, 91%), m.p. 176–177 °C (Found: C, 71.6; H, 6.5; N, 12.7. $C_{20}H_{21}N_3O_2$ requires C, 71.62; H, 6.31; N, 12.53%); δ_H 3.05 (3 H, s, CONMe), 3.23 (3 H, s, CONMe), 3.49 (3 H, s, NMe), 6.29 (1 H, s, imidazole 4-H), and 7.26–7.38 (10 H, m, Ph_2); *m/z* 335 (M^+, 51%), 264 (100), and 105 (100).

1,5-*Dimethylimidazole* (**21**).—Iodomethane (20.1 mmol) was added to the 5-lithio derivative of compound (**14**) (9.9 mmol) generated as in the preparation of (**15**). The mixture was stirred at −78 °C for 10 min and then, with the cooling bath removed, for 15 min; it was then extracted with 2M aqueous hydrogen chloride (5 ml × 8). The combined acidic solutions were washed with diethyl ether (50 ml × 4) and made basic with 20%

* Attempted purification of a portion by distillation *in vacuo* led to decomposition.

† M^+ Was not detected.

aqueous sodium hydroxide. Saturation of the aqueous solution with sodium chloride and its extraction with ethyl acetate (40 ml × 5) gave 1,5-dimethyl-*N*,*N*-dimethylimidazole-2-carboxamide (**16**) (1.58 g, 96%) which was used without further purification.

The 5-methyl derivative (**16**) (0.69 g, 4.1 mmol) was boiled under reflux with 40% aqueous potassium hydroxide (2 ml) for 6 h. The solution was cooled, neutralised, and extracted with ethyl acetate (10 ml × 5) and then with trichloromethane (10 ml × 5) to give (**21**) (0.05 g, 12%): δ_H 2.16 (3 H, s, 5-Me), 3.52 (3 H, s, NMe), 6.78 (1 H, s, imidazole 4-H), and 7.40 (1 H, s, imidazole 2-H); *m*/*z* 96 (M^+, 100%).

5-*Chloro*-1-*methyl*-N,N-*dimethylimidazole*-2-*carboxamide* (**17**).—Reaction of the 5-lithio derivative of (**14**) (12.9 mmol) with *N*,*N*-dimethylsulphamoyl chloride (20.5 mmol) gave, after work-up, the chloro derivative (**17**) as an oil (2.29 g, 95%), b.p. 62 °C/0.65 mmHg which solidified on cooling (m.p. 74–77 °C). A sample for analysis was recrystallised from ethyl acetate–hexane, m.p. 77–79 °C: δ_H 3.07 (3 H, s, CONMe), 3.34 (3 H, s, CONMe), 3.78 (3 H, s, NMe), and 6.98 (1 H, s, imidazole 4-H); *m*/*z* 187.0523 (M^+, 28%; $C_7H_{10}ClN_3O$ requires 187.0513), 130 (100), 116 (100), and 44 (100).

N,N-*Di-isopropyl*-1-*methyl*-5-(1-*methylimidazol*-2-*ylcarbonyl*)*imidazole*-2-*carboxamide* (**20**).—To a solution of the 2-carboxylate (**18**) (0.1 g, 0.7 mmol) in THF (1 ml) at −78 °C was added LDA (0.9 mmol) in THF (1 ml) at −78 °C. The mixture was stirred at −78 °C for 15 min, followed by work-up to give (**20**) (20.7 mg, 19%), m.p. 167–169 °C (from ethyl acetate–hexane); δ_H 1.17 (6 H, d, *J* 6.4 Hz, $CHMe_2$), 1.52 (6 H, d, *J* 6.4 Hz, $CHMe_2$), 3.52–3.65 (2 H, m, CH), 3.96 (3 H, s, NMe), 4.03 (3 H, s, NMe), 7.10 (1 H, d, *J* 0.9 Hz, imidazole 5-H), 7.20 (1 H, d, *J* 0.9 Hz, imidazole 4-H), and 8.40 (1 H, s, imidazole 4-H); *m*/*z* 317.1854 (M^+, 8%, $C_{16}H_{23}N_5O_2$ requires 317.1851) and 217 (100).

Bis(1-*methylimidazol*-2-*yl*) *Ketone* (**22**).—Butyl-lithium in hexane (48.3 mmol) was added to a solution of 1-methylimidazole (3.61 g, 43.9 mmol) in THF (30 ml) at −78 °C. The mixture was stirred at −78 °C for 1 h and dimethyl carbonate (50.0 mmol) added. Work-up of the reaction mixture after 30 min gave the *ketone* (**22**) (3.88 g, 93%), m.p. 155–156 °C (from trichloromethane–hexane) (Found: C, 56.7; H, 5.2; N, 29.3. $C_9H_{10}N_4O$ requires C, 56.83; H, 5.30; N, 29.46%); δ_H 4.02 (6 H, s, NMe), 7.10 (2 H, d, *J* 0.7 Hz, imidazole 5-H), and 7.32 (2 H, d, *J* 0.7 Hz, imidazole 4-H); *m*/*z* 190 (M^+, 63%) and 82 (100).

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