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N-Quaternary Compounds. XXXVII.[1] Syntheses and Reactions of Pyrid-2-thiones with α-Bromoacrylic Acid

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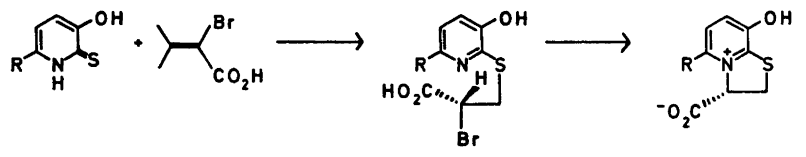
Syntheses of 6-ethyl- and 6-isopropyl-3-hydroxypyrid-2-thiones are described. The syntheses involve a series of reaction steps from a common α-picolinic acid precursor. The relative reactivities of some pyrid-2-thiones towards α-bromoacrylic acid have been investigated.

Further studies of the reaction between pyrid-2-thiones and α,β-unsaturated carbonyl compounds (Scheme 1) required for comparative purposes preparation of pyrid-2-thiones substituted in the 6-position. In previous studies the pyridine has carried a methyl group or a hydrogen atom in the 6-position.[2,3] Syntheses of the ethyl (*1c*) and isopropyl (*1d*) pyrid-2-thiones are herein described. These have been used for investigation of the relative reaction rate as Michael addends to α-bromoacrylic acid.

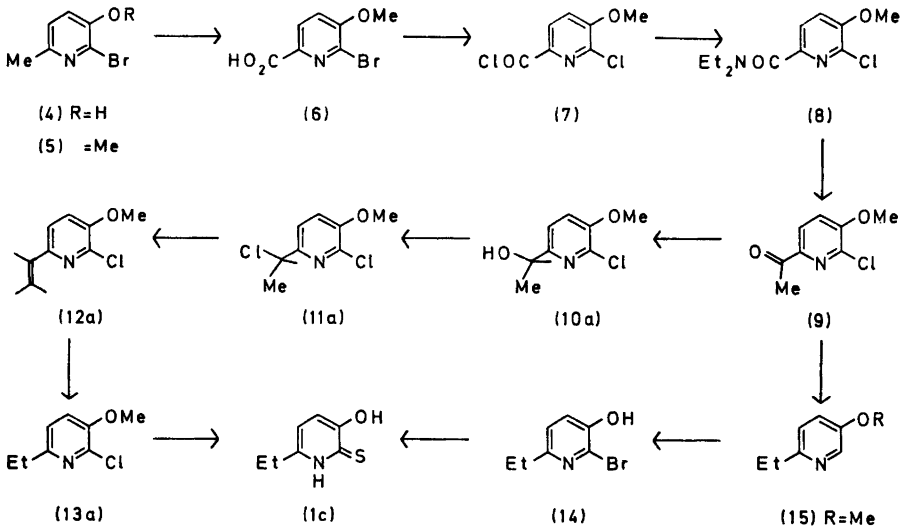
3-Hydroxypyridines are key intermediates in the syntheses of pyrid-2-thiones. Electrophilic substitution such as halogenation goes preferentially into the 2-position.[4] The halogen thus introduced is in an activated pyridine position and is replaceable by nucleophilic sulfur. In the present work 3-hydroxy-6-methylpyridine was brominated almost quantitatively in the 2-position (*4*) in aqueous HBr on addition of hydrogen peroxide. Thiation to (*1b*) was carried out by means of potassium hydrogen sulfide [4] or phosphorus pentasulfide.[5,6] In the case of the 3-alkoxy derivatives (5), choice of experimental conditions can be made such that thiation alone or thiation with concurrent cleavage of the alkoxy group occur.[6] The latter has been made use of in the below syntheses (Schemes 2 and 3).

In the syntheses of 6-substituted 3-hydroxypyridines substituted furfurals or furoic acids are convenient starting points [7] provided the desired 5-substituted furans are readily accessible. As several steps are involved in the syntheses of the desired compounds from these sources, we have instead looked at readily available pyridines. The synthesis of 3-hydroxy-6-ethylpyridine (*16*) from 3-nitro-6-chloropyridine was first repeated.[8] The chlorine was nucleophilically displaced by means of the sodium salt of diethyl methylmalonate followed by decarboxylations to 3-nitro-6-ethylpyridine. After reduction, the amino group was diazotised and the diazonium salt hydrolysed to (*16*). In our hands the diazotisation and hydrolysis proved preparatively unsatisfactory. Instead another synthetic route was worked out in which the bromo acid (*6*) (Scheme 2) is a common starting material for both the ethyl and



(1a) R=H (2) (3a) R=H
(b) =Me (b) =Me
(c) =Et (c) =Et
(d) =i-Prop. (d) =i-Prop.

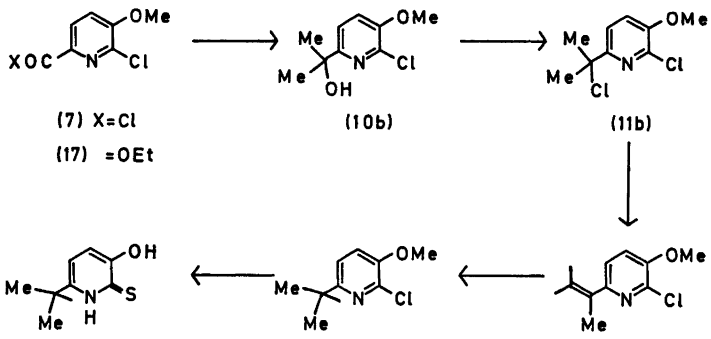
Scheme 1.



Scheme 2.

sopropyl series. For oxidation of the 6-methyl group by potassium permanganate the phenolic OH-group was protected by *O*-methylation. The choice of methyl as the *O*-protecting group was directed by the findings mentioned above that alkyl-aryl ethers are readily cleaved by the thiating agent and that the methoxy group is not affected by the reagents used in the intermediate steps. It was noticed during the preparation of the acid chloride from the acid (*6*) by means of thionyl chloride that partial halogen interchange took place in the pyridine ring. The halogen interchange was reduced but not overcome by heating the acid for a short time in thionyl chloride. The further reactions for the syntheses of the pyrid-2-thiones according to Schemes 2 and 3, may be run on products with partially interchanged halogens. For analytical purposes, however, the reactions herein described (Scheme 2) were run on the chloro compounds. Complete chlorine-bromine interchange was achieved (*7*) by heating the acid chloride of (*6*) in thionyl chloride for 4 d. Amination followed by the Grignard reaction on the amide (*8*) furnished the methyl ketone (*9*). The reaction with methylmagnesium iodide in ether was carried out at ice-bath temperature. The crude product contained about 10 % of the isopropyl alcohol (*10b*) which was removed on crystallisation. Clemmensen reduction of the ketone (*9*) resulted in hydrogenolysis of the chlorine (*15*). HBr was used to cleave the ether (*15*) and the hydroxy derivative (*16*) was brominated and thiated as described above. In a preferential alternative method the ketone (*9*) was reduced to the hydroxy derivative (*10a*) by means of sodium borohydride. Acid catalysed water elimination from (*10a*) was found difficult to effect. Instead (*10a*) was chlorinated by means of thionyl chloride. HCl elimination from (*11a*) to the vinyl pyridine (*12a*) was achieved by means of potassium *tert*-butoxide. The double bond was saturated by hydrogenation at atmospheric pressure over platinum oxide without significant hydrogenolysis of the chlorine. The thiation of the ethyl derivative (*13a*) was carried out by means of phosphorus pentasulfide under conditions which gave concurrent cleavage of the alkyl-oxygen ether linkage and formation of (*1c*).

A very similar approach to the synthesis of the isopropylpyrid-2-thione (*1d*) was used (Scheme 3) starting from the 6-carboxylic acid (*6*). The latter was initially converted to the ethyl ester (*17*) which was subjected to the Grignard reaction. This reaction required heating in ether which led to extensive dehalogenation in the pyridine ring. With the reactive acid chloride (*7*), however, the reaction proceeded smoothly at ice-bath temperature to the tertiary hydroxy compound (*10b*). As for the ethyl analogue (*10a*) acid catalysed water elimination



Scheme 3.

from (*10b*) was unsatisfactory and (*10b*) was chlorinated by means of thionyl chloride. In aqueous potassium hydroxide (*11b*) was converted to the propene (*12b*) which was selectively reduced to the isopropyl derivative (*13b*) on catalytic hydrogenation. Thiation by means of phosphorus pentasulfide finally furnished the hydroxy-thione (*1d*).

In the Michael addition of pyrid-2-thiones to α-bromoacrylic acids a methyl group in the pyridine 6-position causes a rate enhancement relative to the desmethyl analogues.[2] The overall reaction rates for the thiones (*1*) were investigated by competitive reactions in ethyl acetate with α-bromoacrylic acid in the cold. The precipitated HBr-salts of the dihydrothiazolo[3,2-*a*]pyridium products (*3*) were collected when the total yield corresponded to about 15 % and analysed by NMR (100 MHz). Slight solubility differences and partially overlapping of NMR signals made the figures obtained no more than qualitative. With reference to the standard (*1b*) the relative reaction rate for the desmethyl analogue (*1a*) was 0.3 and the rates for the other 6-substituted pyridines (*1c*, *1d*) approximately as for the standard (*1b*).

The overall reaction (Scheme 1) involves firstly adduct formation (*2*) and then cyclisation (*3*). The intermediate adduct (*2*) was not seen. In the cyclisation of (*2*) increasing steric interaction in the series (*1b*) to (*1d*) would be expected between the 6-substituent and the substituents on the side-chain carbon atom involved in the cyclisation reaction. In the adduct formation steric interaction from the 6-substituents is presumably not very different within the series and the alkyl groups exert similar inductive activation. The closely related overall reaction rates for the alkyl derivatives therefore suggest that the intramolecular cyclisation reaction is considerably faster than the intermolecular adduct formation. The rate differences for the two steps are such that the steric decrease in the cyclisation rate with increasing bulkiness of the substituents does not decrease the rate of cyclisation below that of adduct formation.

EXPERIMENTAL

All NMR spectra were determined on a Varian 60 MHz A-60 A spectrometer.

2-Bromo-3-hydroxy-6-methylpyridine (4). 3-Hydroxy-6-methylpyridine (21.8 g, 0.2 mol) was dissolved in 48 % HBr (100 ml, 0.88 mol) and the solution cooled to 0 – 5 °C and kept at this temperature during the ensuing reaction. Hydrogen peroxide (15 %, 50 ml, 0.22 mol) was added slowly with stirring to the cooled solution. The stirring was continued for another 2 h at 0 – 5 °C after the addition was complete. The precipitated product was then filtered off, the filtrate concentrated and the new precipitate collected. The combined product was dissolved in water and the solution neutralised with ammonia. The title compound was precipitated and obtained in more than 90 % yield; and having properties as previously described.[4]

2-Bromo-3-methoxy-6-methylpyridine (5). 2-Bromo-3-hydroxy-6-methylpyridine (188 g, 1 mol) and methyl iodide (200 g, 1.4 mol) were added to 1 M sodium methoxide in methanol (1 l). The mixture was heated under reflux overnight, more of the 1 M sodium methoxide solution (250 ml) and methyl iodide (50 g, 0.35 mol) added and the reaction mixture heated under reflux for another 3 h. The precipitated salt was filtered off from the cold reaction mixture, the filtrate evporated, the residue suspended in 0.1 M NaOH (300 ml) and the title compound extracted into ether. The etheral solution was washed and dried and yielded the title compound in 74 % yield (149 g) on evaporation; properties as previously described.[9]

2-Bromo-3-methoxypyridine-6-carboxylic acid (6). Potassium permanganate (47.4 g, 0.3 mol) was added gradually over 4 h to a suspension of 2-bromo-3-methoxy-6-methylpyridine (20.2 g, 0.1 mol) in water (1 l) at 70 °C. Towards the end of the reaction the temperature was raised to 85 – 90 °C. Methanol (20 ml) was then added to decompose any excess potassium permanganate and the reaction mixture filtered warm. The manganese dioxide filtered off was washed 3 – 4 times with boiling, dilute methanol (1:1) and the combined washings and filtrate concentrated to about half its volume before acidification with HCl. The white carboxylic acid precipitated was recrystallised from dilute ethanol (1:5); yield 16.5 g (71 %), m.p. 245 – 247 °C. (Found: C 36.31; H 2.61; N 6.01. Calc. for $C_7H_6BrNO_3$: C 36.24; H 2.61; N 6.04), τ(TFA) 5.6 (OMe), 1.1 and 1.6 (H-4, H-5).

2-Chloro-3-methoxypyridine-6-carbonyl chloride (7). A solution of 2-bromo-3-methoxypyridine-6-carboxylic acid (11.6 g, 0.05 mol) in thionyl chloride (300 ml) was heated under reflux for 4 d. The solution was then evaporated and the residue triturated with acetonitrile. There remained 6.0 g (58 %) of the title compound sufficiently pure for further reaction. For elemental analysis part of the product was recrystallised from acetonitrile, m.p. 126°C. (Found: C 40.82; H 2.45. Calc. for $C_7H_6ClNO_2$ C 40.81; H 2.45), τ($CDCl_3$) 6.0 (OMe), 1.9 and 2.7 (H-4, H-5).

*2-Chloro-3-methoxypyridine-6-*N,N*-diethylcarboxamide (8).* Diethylamine (5.5 g, 0.075 mol) was added dropwise with stirring to an ice-cold solution of 2-chloro-3-methoxypyridine-6-carbonyl chloride (5.1 g, 0.025 mol) in toluene (250 ml). The reaction mixture was left overnight, the precipitated salt removed by filtration and the filtrate evaporated. Recrystallisation of the residue from diisopropyl ether gave the amide m.p. 60 – 62 °C, yield 5.5 g (90 %). (Found: C 54.40; H 6.15. Calc. for $C_{11}H_{15}ClN_2O_2$: C 54.44; H 6.23), τ($CDCl_3$), 6.1 (OMe), 6.5 and 8.8 (*N*-Et_2), 2.4 and 2.8 (H-4, H-5).

2-Chloro-3-methoxy-6-acetylpyridine (9). A Grignard solution in anhydrous ether (50 ml), prepared from magnesium turnings (0.5 g, 0.022 mol) and methyl iodide (3.1 g, 0.022 mol), was added dropwise to an ice-cold, stirred solution of 2-chloro-3-methoxypyridine-6-*N*,*N*-diethylcarboxamide (4.8 g, 0.02 mol) in anhydrous ether (200 ml). The reaction was run under nitrogen. The reaction was stirred for 1 h after the addition had been completed and the reaction mixture then poured onto ice with some acetic acid. The ether layer was separated, the aqueous layer extracted with ether and the etheral solutions dried and evaporated. The product thus obtained contained about 10 % of the corresponding tertiary alcohol (*10b*). The latter was readily removed by crystallisation from ethanol in which the ketone is very little soluble in the cold; yield 2.3 g (62 %), m.p. 103 – 104 °C. (Found: C 51.98; H 4.42. Calc. for $C_8H_8ClNO_2$: C 51.77; H 4.34), τ($CDCl_3$) 7.3; τ(CH_3CO) 6.0 (OMe), 2.0 and 2.7 (H-4 and H-5).

2-Chloro-3-methoxy-6-(1-hydroxyethyl)pyridine (10a). Sodium borohydride (0.6 g, 0.015 mol) was added gradually to a methanolic solution (50 ml) of 2-chloro-3-methoxy-6-acetylpyridine (0.9 g, 0.005 mol). The solution was evaporated after 1 h, the residue triturated with water and the pH adjusted to about 7 before chloroform extractions. Evaporation of the dried chloroform extracts gave the title compound 0.8 g, 90 %), m.p. 35 – 37 °C. The product was sufficiently pure for elemental analysis. (Found: C 51.25; H 5.42. Calc. for $C_8H_{10}ClNO_2$: C 51.21; H 5.37), τ($CDCl_3$) 8.5 (3 H, d, CH_3C), 6.1 (OMe), 5.2 (H, q, CH-Me), 2.8 (2 H, broad singlet, H-4 and H-5).

2-Chloro-3-methoxy-6-(1-chloroethyl)pyridine (11a). 2-Chloro-3-methoxy-6-(1-hydroxyethyl)-pyridine (0.8 g, 0.004 mol) was kept in thionyl chloride (30 ml) overnight. Evaporation left the title compound. The chlorination is quantitative and the product can be used directly in the next step. For analysis part of the product was dissolved in chloroform, this solution washed well with water and dried before evaporation. The residual material, after recrystallisation from diisopropyl ether, had m.p. 51 – 53 °C. (Found: C 46.48; H 4.36. Calc. for $C_8H_9Cl_2NO$: C 46.63; H 4.40), τ($CDCl_3$) 8.2 (3 H, d, CH_3C), 6.1 (OMe), 4.9 (H, q, CH – Me), 2.6 and 2.8 (H-4 and H-5).

2-Chloro-3-methoxy-6-methylpyridine (13a). A solution of 2-chloro-3-methoxy-6-(1-chloroethyl)pyridine (0.8 g, 0.004 mol) in 0.5 M potassium *tert*-butoxide in *tert*-butanol (16 ml) was heated at 80 °C for 90 min. Acetic acid (4 ml) was added to the cold reaction mixture until acid pH. The *2-chloro-3-methoxy-6-vinylpyridine (12a)* thus obtained was not isolated but the solution subjected to hydrogenation over platinum oxide at room temperature and atmospheric pressure for 3 h. The catalyst was then removed and the solution evaporated to dryness at reduced pressure. Water was added to the residual material, pH adjusted to about 7 and the title compound extracted into chloroform. Evaporation of the washed and dried chloroform extracts left an oily material, 0.4 g (58 %). For elemental analysis a portion of this material was dissolved in anhydrous ether, and HBF_4 in ether added dropwise. The white, semicrystalline tetrafluoroborate was fully solidified on trituration with acetone; m.p. 166 – 168 °C. (Found: C 36.80; H. 4.30. Calc. for $C_8H_{10}ClNO.HBF_4$: C 37.05; H 4.25), τ(NMR of oily material in $CDCl_3$) 8.7 and 7.3 (Et), 6.1 (OMe), 2.8 and 2.9 (H-4, H-5).

3-Hydroxy-6-ethylpyridine (16). Zinc amalgam was prepared from granulated zinc (5 g) and mercuric chloride (0.6 g) in water (20 ml) and conc. HCl (1 ml). The water solution was decanted after 5 min and dilute HCl (1:1) solution (60 ml) added. 2-Chloro-3-methoxy-6-acetylpyridine (2.4 g, 0.013 mol) was next added and the reaction mixture heated under reflux

for 3 h. The reaction mixture was then neutralised and the compound extracted into ether. The ether was evaporated leaving 3-methoxy-6-ethylpyridine. The latter was dissolved in 48 % HBr in acetic acid (25 ml) and the solution heated for 5 h. Evaporation left the HBr salt which was dissolved in a minimum amount of water and the solution neutralised when the title compound was slowly precipitated in 20 % yield; properties as described.[5]

2-Chloro-3-methoxy-(2-hydroxy-2-propyl)pyridine (10b). A solution of methylmagnesium iodide was prepared from magnesium turnings (2.0 g, 0.08 mol) and methyl iodide (11.4 g, 0.08 mol) in anhydrous ether (100 ml) under nitrogen. The acid chloride (*7*) (4.1 g, 0.02 mol) was then added dropwise with stirring to the Grignard solution cooled by ice-water. After completion of the addition the reaction was heated under reflux for 2 h before being poured onto ice containing a little acetic acid. The ether layer was separated, the aqueous layer was extracted with ether and the combined etheral solutions were dried and evaporated. The residual oily material was distilled; yield 3.3 g (82 %), b.p. 116–118 °C/0.15 mmHg. For elemental analysis a portion was crystallised from diisopropyl ether, the crystalline material being collected at −20 °C; m.p. 30–32 °C. (Found: C 53.25; H 5.96. Calc. for $C_9H_{12}ClNO_2$: C 53.61; H 6.00), τ($CDCl_3$) 8.5 (CMe_2, s), 6.1 (OMe), 2.6 and 2.8 (H-4, H-5).

2-Chloro-3-methoxy-6-isopropenylpyridine (12b). A solution of 2-Chloro-3-methoxy-6-(2-hydroxy-2-propyl)pyridine (4.0 g, 0.02 mol) and thionyl chloride (3.5 g, 0.03 mol) in benzene (50 ml) was heated under reflux for 30 min before the benzene was evaporated. The residual halide was added to aqueous 0.5 M potassium hydroxide (80 ml) and the suspension heated under reflux for 2 h. The cold reaction mixture was extracted with ether, the dried ether extracts evaporated and the residual oil distilled; yield 2.6 g (71 %), b.p. 88–90 °C/0.05 mmHg. (Found: C 58.66; H 5.43. Calc for $C_9H_{10}ClNO$: C 58.87; H 5.49), τ(CCl_4) 7.9 (CH_3–C), 6.2 (OMe), 4.3 and 4.9 (=CH_2), 2.8 and 3.0 (H-4, H-5).

2-Chloro-3-methoxy-6-isopropylpyridine (13b). A solution of 2-chloro-3-methoxy-6-isopropenylpyridine (2.2 g, 0.012 mol) in methanol (25 ml) was hydrogenated over 5 % palladium on charcoal (1/2 teaspoon) at 0.38 MPa* and room temperature. The catalyst was filtered off after 4 h, the solvent evaporated and the residual oil distilled; yield 1.6 g (72 %), b.p. 78–84 °C/0.1 mmHg. (Found: C 57.88; H 6.66. Calc. for $C_9H_{12}ClNO$: C 58.20; H 6.47), τ($CDCl_3$) 8.7 (6H, d, CMe_2) and 7.1 (H, m, CH–CMe_2), 6.1 (OMe), 2.8 and 2.9 (H-4, H-5).

3-Hydroxy-6-isopropylpyrid-2-thione (1d). 2-Chloro-3-methoxy-6-isopropylpyridine (5.6 g, 0.03 mol) and phosphorus pentasulfide (6.7 g, 0.03 mol) were ground well together and the mixture heated at 140 °C for 10 h. The reaction mixture was then decomposed on warming with water and the resultant suspension neutralised with conc. ammonia and extracted several times with chloroform. The residue, after evaporation of the dried chloroform extracts, was dissolved in boiling carbon tetrachloride and some hexane added. The yellow title compound crystallised out from this solution on standing; yield 3.5 g (68 %), m.p. 110–112 °C. (Found: C 56.45; H 6.57; S 19.08. Calc. for $C_8H_{11}NOS$: C 56.77; H 6.55; S 18.95), τ(TFA) 8.6 (6H, d, CMe_2) and 6.9 (H, m, CH–CMe_2), 2.1 and 2.6 (H-4, H-5).

3-Hydroxy-6-ethylpyrid-2-thione (1c) was prepared from (*13a*) and phosphorus pentasulfide as the isopropyl analogue (*1d*) above. The crude thione in chloroform was filtered through a short silica gel column before evaporation. Recrystallisation from toluene gave m.p. 150–151 °C; yield 43 %. (Found: C 53.94; H 6.13. Calc. for C_7H_9NOS: C 54.19; H 5.85), τ($CDCl_3$) 8.7 and 7.3 (Et), 3.0 and 3.5 (H-4, H-5).

In another experiment 3-hydroxy-6-ethylpyridine (*16*) was brominated as described for the 6-methyl analogue (*4*) above and the crude bromo compound (*14*) subjected to thiation as above using phosphorus pentasulfide. The yield in the thiation was 60 %.

8-Hydroxy-5-isopropyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (3d). 3-Hydroxy-6-isopropylpyrid-2-thione (1.7 g, 0.01 mol) and α-bromoacrylic acid (3.0 g, 0.02 mol) in ethyl acetate (66 ml) were stirred at room temperature for 24 h. The precipitated title compound as HBr salt was then filtered off (1.9 g, 59 %). Due to the case of decarboxylation the salt was not attempted recrystallised but washed well with ethyl acetate before elemental analysis; m.p. 195–197 °C (decomp.) (Found: C 41.00, H 4.40. Calc. for $C_{11}H_{14}NO_3S.HBr$: C 41.20; H 4.38, τ(TFA) 8.5 (6H, d, CMe_2) and 6.7 (H, m, CH–CMe_2), 5.7 (2 H-2), 3.5 (H-3), 2.0 and 2.5 (H-7, H-6).

8-Hydroxy-5-ethyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate (3c) *as HBr salt* was formed from 3-hydroxy-6-ethylpyrid-2-thione and α-bromoacrylic acid in 65 % yield under the above reaction conditions in ethyl acetate. Due to the ease of decarboxylation the crude product after being washed well with ethyl acetate was subjected directly for elemental analysis; m.p. 179 °C (decomp.). (Found: C 38.98, H 4.26. Calc. for $C_{10}H_{11}NO_3S.HBr$: C 39.23; H 3.95), τ(TFA) 8.5 and 7.0 (Et), 5.7 (2 H-2), 3.5 (H-3), 2.0 and 2.5 (H-7, H-6).

* 1 MPa ≈ 10.2 kg cm^{-2}.

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