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A Practical Synthesis of α-Aryl Methyl Ketones via a Transition-Metal-Free Meerwein Arylation

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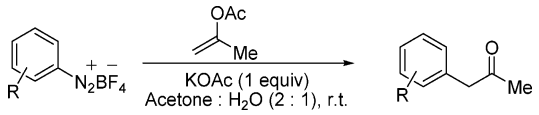

We report herein a simple, scalable, transition-metal-free approach to the synthesis of α-aryl methyl ketones from diazonium tetrafluoroborate salts under mild conditions. This methodology uses easily accessible and nontoxic starting material and was applied to the multi-kilogram-scale preparation of 1-(3-bromo-4-methylphenyl)propan-2-one.

The synthesis of α-aryl ketones remains a challenging problem in organic synthesis. While a number of effective reagents have been developed for the direct arylation of ketones, they usually need to be prepared from toxic and expensive starting materials.[1] In the past decade, several groups have reported more appealing catalytic methodologies using a variety of metals (Pd,[2] Ni,[3] Pb,[4] Cu,[5] and Bi[6]);[7] however, the high cost and air sensitivity of most transition-metal catalysts and ligands plus the additional steps required in order to eliminate residual metals represent major drawbacks for their general application on kilogram-scale chemistry, especially for the preparation of final drug substances. Additionally, only a few isolated examples have been reported for the direct α-arylation of acetone.[2n,o,7e,i] Although very well studied, the copper-catalyzed addition of an aryl diazonium chloride to an activated unsaturated compound (Meerwein arylation)[8] has shown limited use for the preparation of α-aryl carbonyls. Thus, Raucher[8e] reported the synthesis of indoles by reacting 2-nitrobenzene diazonium chlorides with vinyl acetate to give a mixture of α-aryl aldehyde and the corresponding α-chloro acetate. Tanaka[8i] reported the synthesis

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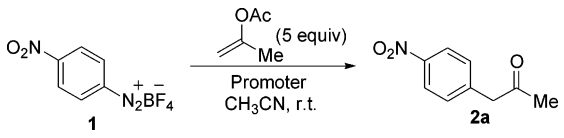
TABLE 1. Effect of Catalysts and Promoters on the Arylation[a]



entry	promoter	assay yield[b] (%)
1	none	0
2	$CuCl_2$ (0.15 equiv)	19
3	$Cu(OTf)_2$ (0.15 equiv)	29
4	CuO (0.15 equiv)	16
5	Cu_2O (0.15 equiv)	14
6	$CuSO_4$ (0.15 equiv)	25
7	$FeSO_4-7H_2O$ (0.15 equiv)	23
8	$Pd(OAc)_2$ (0.15 equiv)	19
9	KO_2 (1.1 equiv)	27
10	KO_2CCF_3 (1.1 equiv)	48
11	CsOAc (1.1 equiv)	46
12	NaOAc Buffer (pH 4.5) (1.1 equiv)	44
13	NaOAc Buffer (pH 3.0) (1.1 equiv)	34
14	NaOAc (1.1 equiv)	53
15	KOAc (1.1 equiv)	53

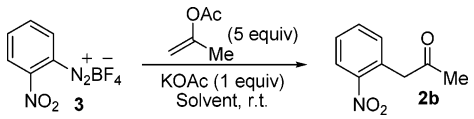
[a] To a stirred solution of the diazonium salt and isopropenyl acetate in CH_3CN at rt was added the promoter and the reaction quenched after 2 h. [b] Determined by HPLC analysis vs authentic standard.

of α-aryl aryl ketones from arene diazonium salts and silyl enol ethers of aryl ketones in pyridine. It is worth noting that these last methods using diazonium salts do not report the transition-metal-free synthesis of α-aryl *alkyl* ketones. A recent synthetic challenge has prompted us to develop a new, inexpensive, and scalable methodology for the arylation of an acetone derivative. We felt that an attractive approach to the synthesis of α-aryl methyl ketones would be available through a modification of the Meerwein arylation. Furthermore, anilines are generally cost-effective starting materials from which aryl diazonium tetrafluoroborate salts are simple to prepare.[9] This paper highlights our findings on a catalytic and transition-metal free approach for the synthesis of α-aryl methyl ketones under mild conditions using diazonium tetrafluoroborate salts and isoproprenyl acetate, a readily available and nontoxic starting material.

Our investigations of the reaction started with the studies of the effect of several Cu, Fe, and Pd catalysts on the arylation of isopropenyl acetate with 4-nitrobenzenediazonium tetrafluoroborate (**1**) in acetonitrile at rt to give 4-nitrophenylacetone (**2a**) (Table 1, entries 2−8). Although the reaction does proceed in each case, the yields were relatively low (14−29%), and several side reactions were observed. We next turned our attention to transition-metal-free promoters (Table 1, entries 9−15). We were delighted to find that nucleophilic promoters were efficient mediators of the arylation, obviating the need for transition metals. Thus, acetate and trifluoroacetate salts were observed to be efficient promoters for the arylation reaction (Table 1, entries 10−15). A marginal pH dependence was observed for this reaction[10] as demonstrated when the reactions were carried out in buffered acetate solutions (Table 1, entries 12 and 13). From this screen, NaOAc and KOAc emerged as the most efficient promoters of the reaction affording 2-nitrophenylacetone in 53% yield (Table 1, entries 14 and 15).[11]

In order to demonstrate this chemistry on a wider range of substrates such as synthetically useful indole precursors, 2-nitrobenzene diazonium tetrafluoroborate (**3**) was also investigated as a substrate in this reaction (Table 2). However, using the two best solvents from a previous solvent screen (acetonitrile and acetone),[12] disappointing assay yields were observed (Table 2, entries 1 and 2). Since KOAc is only sparingly soluble in both acetone and acetonitrile we introduced water as a cosolvent in order to homogenize the reaction mixture and found that an acetone/water mixture of 2:1 increased our assay yield significantly (Table 2, entry 3 vs 2). We found that a slow addition of an aqueous solution of KOAc over 2 h afforded an improved assay yield of the desired ketone **2b** (Table 2, entry 4 vs 3). Furthermore, the slow addition allowed for a safe control of the reaction rate and nitrogen gas evolution as well as a significant decrease in the amount of byproducts generated.

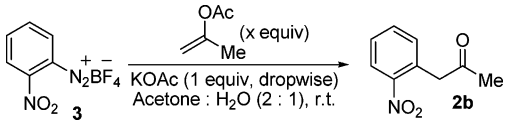
TABLE 2. Effect of Solvents and Rate of Addition on the Arylation



entry	solvent	assay yield[a] (%)
1	CH_3CN	23
2	acetone	10
3	acetone/H_2O (2:1)[b]	56
4	acetone/H_2O (2:1)[c]	65

[a] Determined by HPLC analysis vs authentic standard. [b] KOAc was added in one portion. [c] KOAc solution in H_2O was added dropwise over 2 h.

TABLE 3. Effect of the Stoichiometry of Isopropenyl Acetate on the Arylation



entry	equiv	assay yield[a] (%)
1	1	30
2	5	65
3	10	75
4	20	93
5	50	79

[a] Determined by HPLC analysis vs authentic standard.

Finally, examination of the isopropenyl acetate stoichiometry revealed that an increase in the number of equivalents from 1 to 20 resulted in a dramatic increase in the assay yield (Table 3, entries 1−4).[13] A further increase to 50 equiv resulted in a decrease in assay yield, presumably due to solubility issues (Table 3, entry 5).

We next applied these conditions to a variety of diazonium tetrafluoroborate salts[9] (Table 4). The reaction is tolerant of several functional groups. A series of 2-arylnitrodiazonium species can be arylated to provide 2-nitrophenylacetones, precursors for indole synthesis (Table 4, entries 1−5). A series of α-aryl methyl ketones containing other functional groups such as cyano, ester, Cl, and CF_3 can also be synthesized (Table 4, entries 6−12).

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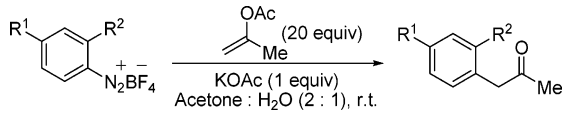
(11) No residual metals were detected in KOAc when tested by ICPMS.

(12) Other solvents tested on the arylation of isopropenyl acetate with 2-nitro-4-(trifluoromethoxy)aniline include: THF, DCE, toluene, chlorobenzene, benzonitrile, *t*-BuOH, *t*-BuCN, CF_3CH_2OH. Yields varied between 0−35.%.
(13) Isopropenyl acetate is available at $40/kg from several suppliers.

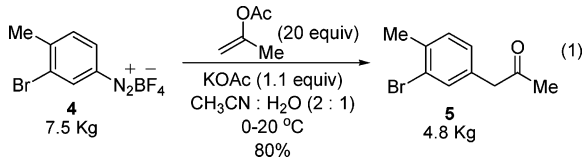
TABLE 4. Synthesis of Various α-Aryl Methyl Ketones



entry	R^1	R^2	yield[a] (%)	product
1	H	NO_2	76	**2b**
2	CF_3	NO_2	65	**2c**
3	CH_3	NO_2	60	**2d**
4	OCF_3	NO_2	34	**2e**
5	OCH_3	NO_2	13	**2f**
6	NO_2	H	58	**2a**
7	Cl	H	70	**2g**
8	CF_3	H	71	**2h**
9	H	CN	72	**2i**
10	H	CO_2Me	58	**2j**
11	CF_3	Cl	62	**2k**
12	CH_3	H	39	**2l**

[a] Isolated yield after column chromatography.

Finally, we required multi-kilogram quantities of 1-(3-bromo-4-methylphenyl)propan-2-one (**5**) as part of an ongoing drug discovery program in our laboratories. This newly developed methodology is a viable process for multi-kilogram quantities synthesis of α-aryl methyl ketone **5**. Thus, large quantities of the starting materials and solvents required are common easily accessible chemicals and the 3-bromo-4-methyldiazonium tetrafluoroborate salt (**4**) is a bench stable solid at rt.[14,15] The transition-metal free synthesis of 4.8 kg of α-aryl methyl ketone **5** was completed in a safe and inexpensive manner using the developed methodology (eq 1).



In conclusion we have described a new transition-metal free approach to the synthesis of α-aryl methyl ketones from diazonium tetrafluoroborate salts and isopropenyl acetate under mild conditions. This methodology is simple, scalable, environmentally friendly and was demonstrated safely on multi-kilogram amounts in the preparation of 1-(3-bromo-4-methylphenyl)propan-2-one.

(14) Diazonium ions are known to exhibit unstable characteristics that can cause some salts to be explosive. The reactivity of each individual diazonium compound should be investigated to determine their explosive potential before running large scale experiments.

(15) The dried diazonium salt intermediate has an exotherm of 35.8 cal/g initiating at 100 °C and a smaller exotherm of 3.5cal/g initiating at 175 °C as measured by DSC. Therefore, it is considered a stable intermediate at rt.

(16) Strazzolini, P.; Giumanini, A. G.; Runcio, A.; Scuccato, M. *J. Org. Chem.* **1998**, *63*, 952.

Experimental Section

2-Nitrophenylacetone[16] **(2b).** To a stirred solution of isopropenyl acetate (4.4 mL, 40 mmol) in acetone (13 mL) and water (7 mL) was added 0.1 mL of a solution of KOAc (200 mg, 2 mmol) in water (1 mL) followed by 2-nitrobenzenediazonium tetrafluoroborate (474 mg, 2 mmol). Then, the rest of the aqueous KOAc solution was added dropwise over 2 h and stirred overnight. The reaction mixture was diluted with MTBE and water, and the layers were separated. The aqueous layer was back-extracted with MTBE. The combined organic extracts were washed with aqueous saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography on silica gel with hexane/EtOAc (3:1) to provide 244 mg (76%) of **2b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1 H, d, J = 8.0 Hz), 7.61 (1 H, t, J = 7.0 Hz), 7.48 (1 H, t, J = 7.3 Hz), 7.30 (1 H, d, J = 7.6 Hz), 4.14 (2 H, s), 2.34 (3 H, s).

1-(3-Bromo-4-methylphenyl)propan-2-one (5). A visually clean 160 L cylindrical reactor equipped with a mechanical stirrer, a dropping funnel, and a N_2 inlet and outlet was charged with isopropenyl acetate (57.4 L, 526 mol), 3-bromo-4-methylbenzenediazonium tetrafluoroborate salt (**4**) (7.5 kg, 26.3 mol), acetonitrile (37.5 L), and water (3.75 L). The light yellow slurry was cooled to an internal temperature of 0−4 °C, and a solution of KOAc (2.85 kg, 29.0 mol, 110 mol %) in water (3.75 L) was added over 3 h. *Caution: Gas evolution, proper venting required!!* The internal temperature rose to 15−18 °C. The batch was allowed stir 30 min and N_2 evolution ceased. Water (37.5 L) was added, and the layers were cut. The upper organic layer was washed with brine (18.75 L) and then concentrated under vacuum. HPLC analysis: 4.8 kg, 80% assay yield. An analytical sample was obtained by distillation under vacuum (clear oil, bp 113 °C, 0.4 mmHg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (1H, s), 7.20 (1H, d, J = 8 Hz), 7.05 (1H, d, J = 8 Hz), 3.65 (2H, s), 2.38 (3H, s), 2.11 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 136.5, 133.3, 133.0, 130.9, 128.2, 124.9, 49.7, 29.3, 22.4; HRMS ESI (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{12}{}^{81}$BrO 227.0065, found 227.0066.

1-(3-Bromo-4-methylphenyl)propan-2-one (5) on a Preparative Scale. 3-Bromo-4-methylbenzenediazonium tetrafluoroborate salt (**4**) (75 g, 263 mmol) was suspended in acetonitrile (375 mL) and water (37.5 mL). The slurry was cooled to 0−5 °C, and isopropenyl acetate (574 mL, 5.26 mol) was added. A solution of KOAc (28.4 g, 289.3 mmol) in water (37.5 mL) was added over 2 h. *Caution: Gas evolution, proper venting required!!* The solution was allowed stir for 30 min, and N_2 evolution ceased, water was added, and the layers were separated. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to afforded ketone **5** as a red oil (78−80% HPLC assay yield).

Supporting Information Available: Experimental procedures and spectroscopic data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information to Accompany

Practical Synthesis of α-Aryl methyl ketones via a Transition-Metal free Meerwein Arylation

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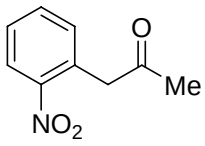
General Information. Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen. All commercially available reagents were used without further purification. The diazonium tetrafluoroborate salts were either commercially available or prepared according to literature.[1] Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on silica gel (230-400 mesh).[2] ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$), unless otherwise noted, on a 400 or 500 MHz instrument. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad) and coupling constant in hertz (Hz). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77 ppm) on the δ scale. High Resolution mass spectra (HMRS) were performed on a high resolution magnetic sector mass spectrometer.

General procedure

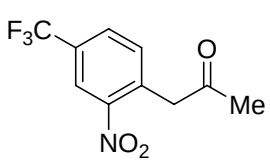


2-nitrophenylacetone[3] **(2b)**: To a stirred solution of isopropenyl acetate (4.4 mL, 40 mmol) in acetone (13 mL) and water (7 mL) was added 0.1 mL of a solution of KOAc (200 mg, 2 mmol) in water (1 mL) followed by 2-nitrobenzenediazonium tetrafluoroborate (474 mg, 2 mmol). Then, the rest of the aqueous KOAc solution was added dropwise over 2 hours and stirred overnight. The reaction mixture was diluted with MTBE and water and the layers were separated. The aqueous layer was back-extracted with MTBE. The combined organic extracts were washed with aqueous saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography on silica gel with Hexane:EtOAc (3:1) to provide 244 mg (76%) of **2b**.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1 H, d, *J* = 8.0 Hz), 7.61 (1 H, t, *J* = 7.0 Hz), 7.48 (1 H, t, *J* = 7.3 Hz), 7.30 (1 H, d, *J* = 7.6 Hz), 4.14 (s, 2 H), 2.34 (s, 3 H).

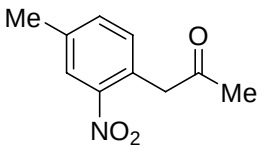
[1] Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572.

[2] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

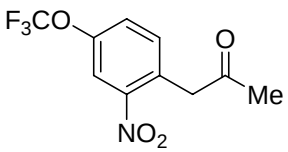
[3] Strazzolini, P.; Giumanini, A. G.; Runcio, A.; Scuccato, M. *J. Org. Chem.* **1998**, *63*, 952.



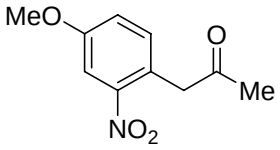
2-Nitro-4-trifluoromethylphenylacetone[4] (**2c**): The general procedure was followed. Isolated 286 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1 H, s), 7.85 (1 H, d, J = 7.6 Hz), 7.46 (1 H, d, J = 7.8 Hz), 4.25 (2 H, s), 2.36 (3 H, s).



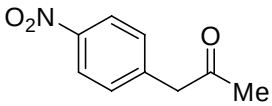
2-Nitro-4-methylphenylacetone (**2d**): The general procedure was followed. Isolated 205 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (1 H, s), 7.43 (1 H, d, *J* = 7.7 Hz), 7.18 (1 H, d, *J* = 7.7 Hz), 4.10 (2 H, s), 2.47 (3 H, s), 2.35 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 148.4, 138.9, 134.4, 133.3, 127.4, 125.6, 48.2, 29.9, 20.82; HRMS ESI (*m* / *z*): $[M + H]^+$ calcd for $C_{10}H_{12}O_3N$, 194.0810; found 194.0811.



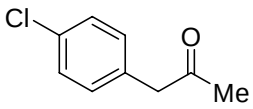
2-Nitro-4-trifluoromethoxyphenylacetone[5] (**2e**): The general procedure was followed. Isolated 162 mg (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1 H, d, *J* = 9.6 Hz), 7.49 (1 H, d, *J* = 8.4 Hz), 7.35 (1 H, d, *J* = 8.4 Hz), 4.17 (2 H, s), 2.35 (3 H, s).



2-Nitro-4-methoxyphenylacetone[6] (**2f**): The general procedure was followed. Isolated 50 mg (13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 2.4 Hz), 7.20-7.14 (2 H, m), 4.06 (2 H, s), 3.91 (3 H, s), 2.33 (3H, s).



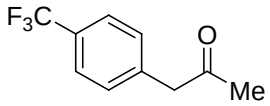
4-Nitrophenylacetone[7] (**2a**): The general procedure was followed. Isolated 188 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (2 H, d, *J* = 8.5 Hz), 7.38 (2 H, d, *J* = 8.5 Hz), 3.87 (2 H, s), 2.26 (3 H, s).



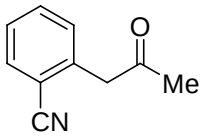
4-Chlorophenylacetone[8] (**2g**): The general procedure was followed. Isolated 212 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

[4] Allais, A.; Meier, J.; Mathieu, J.; Nomine, G.; Peterfalvi, M.; Deraedt, R.; Chifflot, L.; Benzoni, J.; Fournex, R. *Eur. J. Med. Chem. Ther.* **1975**, *10*, 187.
[5] Wong, A.; Kuethe, J. T.; Davies, I. W. *J. Org. Chem.* **2003**, *68*, 9865.
[6] Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem.* Soc. **1988**, *110*, 2242.
[7] Rafizadeh, K.; Yates, K. *J. Org. Chem.* **1984**, *49*, 1500.

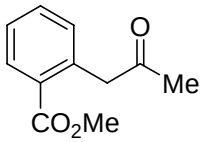
7.33 (2 H, d, *J* = 8.3 Hz), 7.16 (2 H, d, *J* = 8.3 Hz), 3.70 (2 H, s), 2.19 (3 H, s).



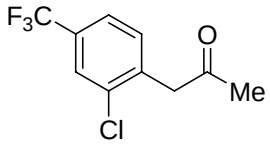
4-Trifluoromethylphenylacetone[9] (**2h**): The general procedure was followed. Isolated 257 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2 H, d, *J* = 7.9 Hz), 7.33 (2 H, d, *J* = 7.9 Hz), 3.79 (2 H, s), 2.21 (3 H, s).



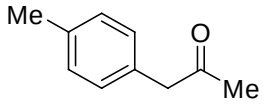
2-Cyanophenylacetone[10] (**2i**): The general procedure was followed. Isolated 207 mg (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1 H, d, *J* = 7.8 Hz), 7.54 (1 H, t, *J* = 7.7 Hz), 7.36 (1 H, t, *J* = 7.6 Hz), 7.29 (1 H, d, *J* = 7.8 Hz), 3.97 (2 H, s), 2.27 (3 H, s).



Methyl 2-(2-oxopropyl)benzoate[11] (**2j**): The general procedure was followed. Isolated 200 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (1 H, d, *J* = 7.8 Hz), 7.49 (1 H, t, *J* = 7.5 Hz), 7.36 (1 H, t, *J* = 7.6 Hz), 7.20 (1 H, d, *J* = 7.6 Hz), 4.11 (2 H, s), 3.86 (3 H, s), 2.28 (3 H, s).



2-Chloro-4-trifluoromethylphenylacetone (**2k**): The general procedure was followed. Isolated 262 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1 H, s), 7.49 (1 H, d, *J* = 8.0 Hz), 7.32 (1 H, d, *J* = 10.4 Hz), 3.93 (2 H, s), 2.26 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 136.9, 135.0, 132.2, 131.1 (q, *J* = 33 Hz), 126.5 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 3.6 Hz), 122.2 (q, *J* = 272 Hz), 48.0, 29.9; HRMS ESI (*m* / *z*): $[M + H]^+$ calcd for $C_{10}H_9OF_3Cl$, 237.0288; found 237.0286.



4-Methylphenylacetone[7] (**2l**): The general procedure was followed. Isolated 104 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (2 H, d, *J* = 8.0 Hz), 7.14 (2 H, d, *J* = 8.0 Hz), 3.69 (2 H, s), 2.38 (3 H, s), 2.18 (3 H, s).

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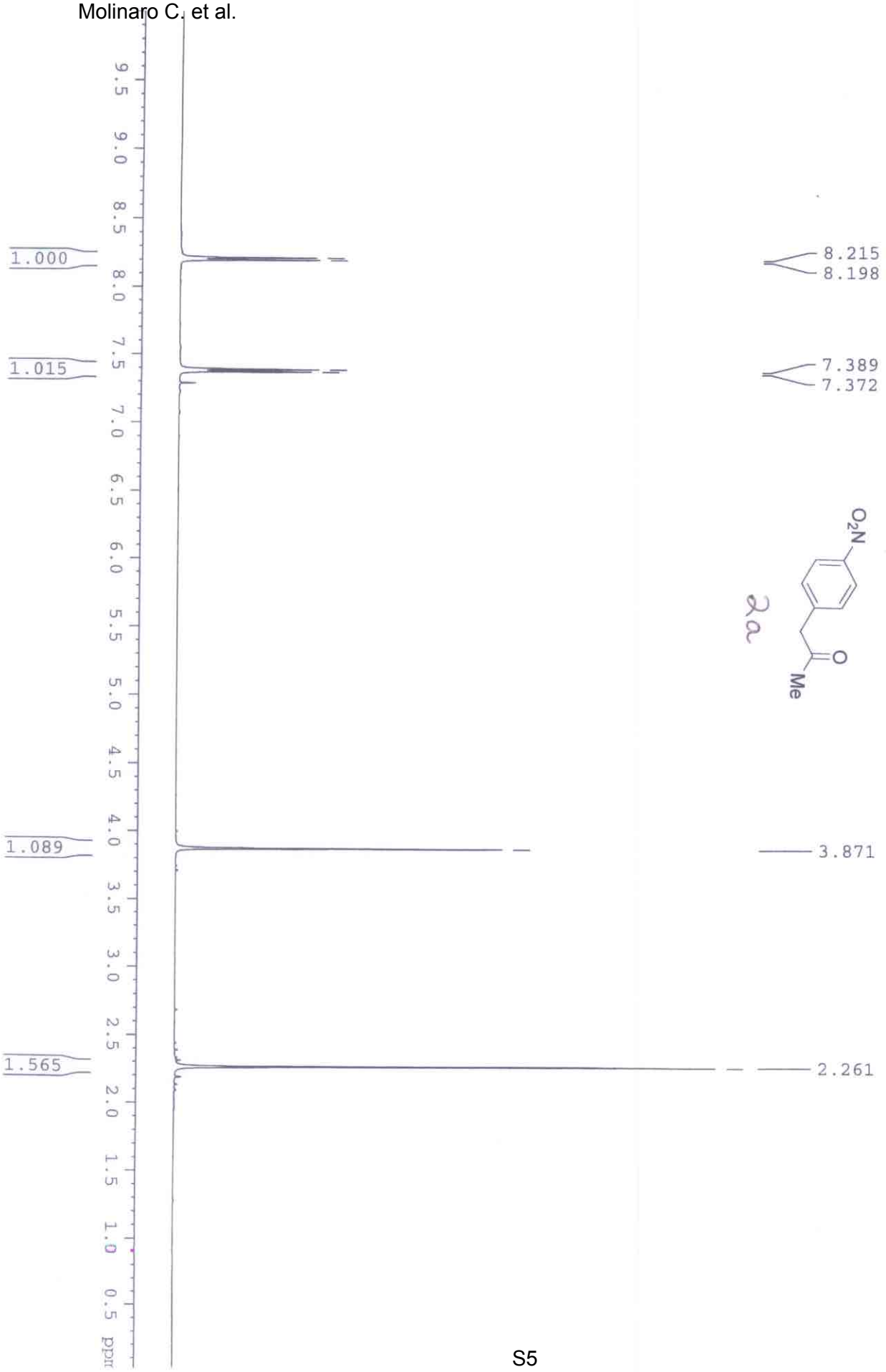
[8] Kurz, M. E.; Baru, V.; Nguyen, P-N. *J. Org. Chem.* **1984**, *49*, 1603.
[9] Owen, J. R.; Saunders, W. H. Jr. *J. Am. Chem. Soc.* **1966**, 88, 5809.
[10] Schubert, T.; Kula, M.-R.; Müller, M. *Synthesis* **1999**, 2045.
[11] Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.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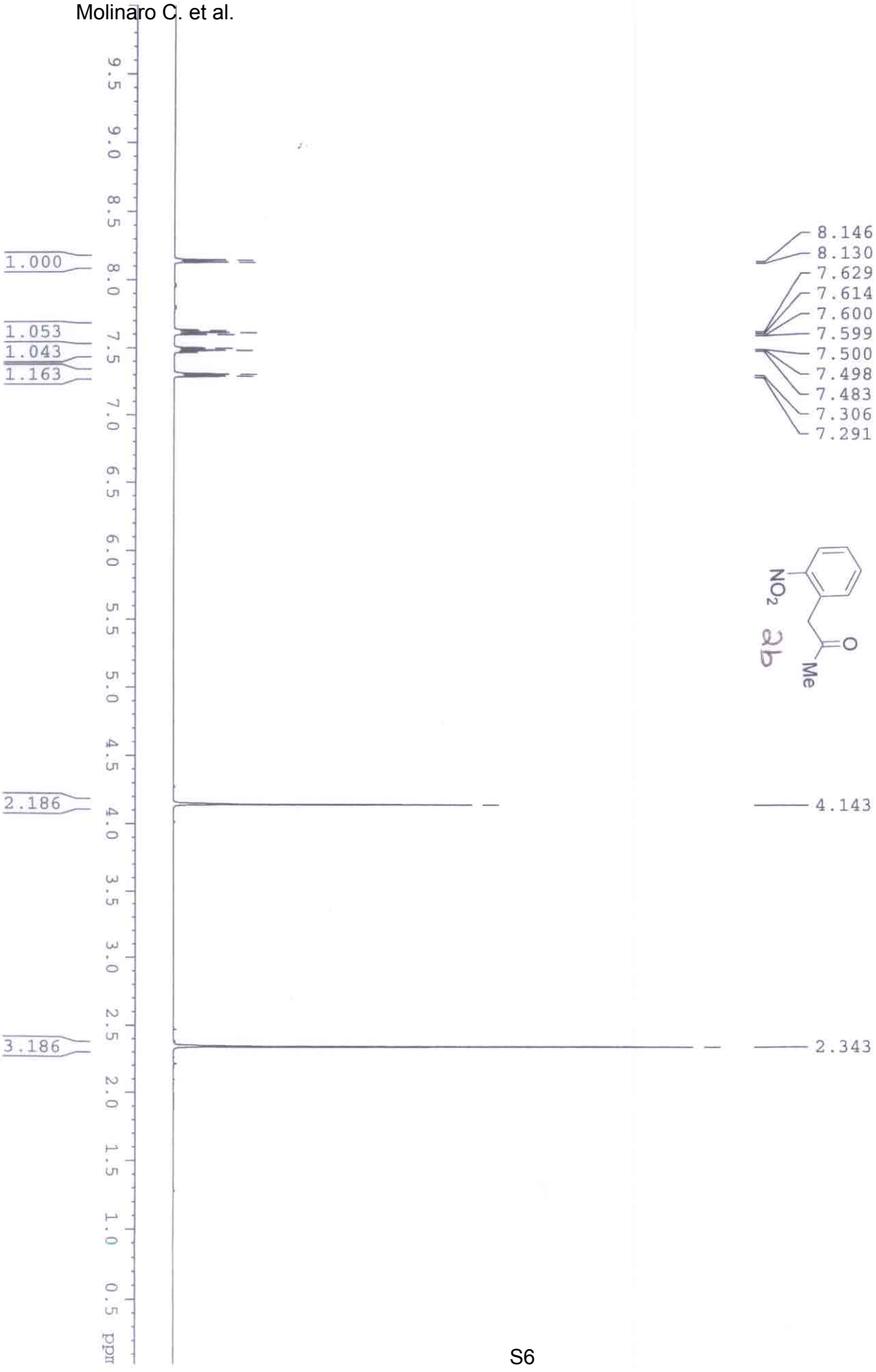
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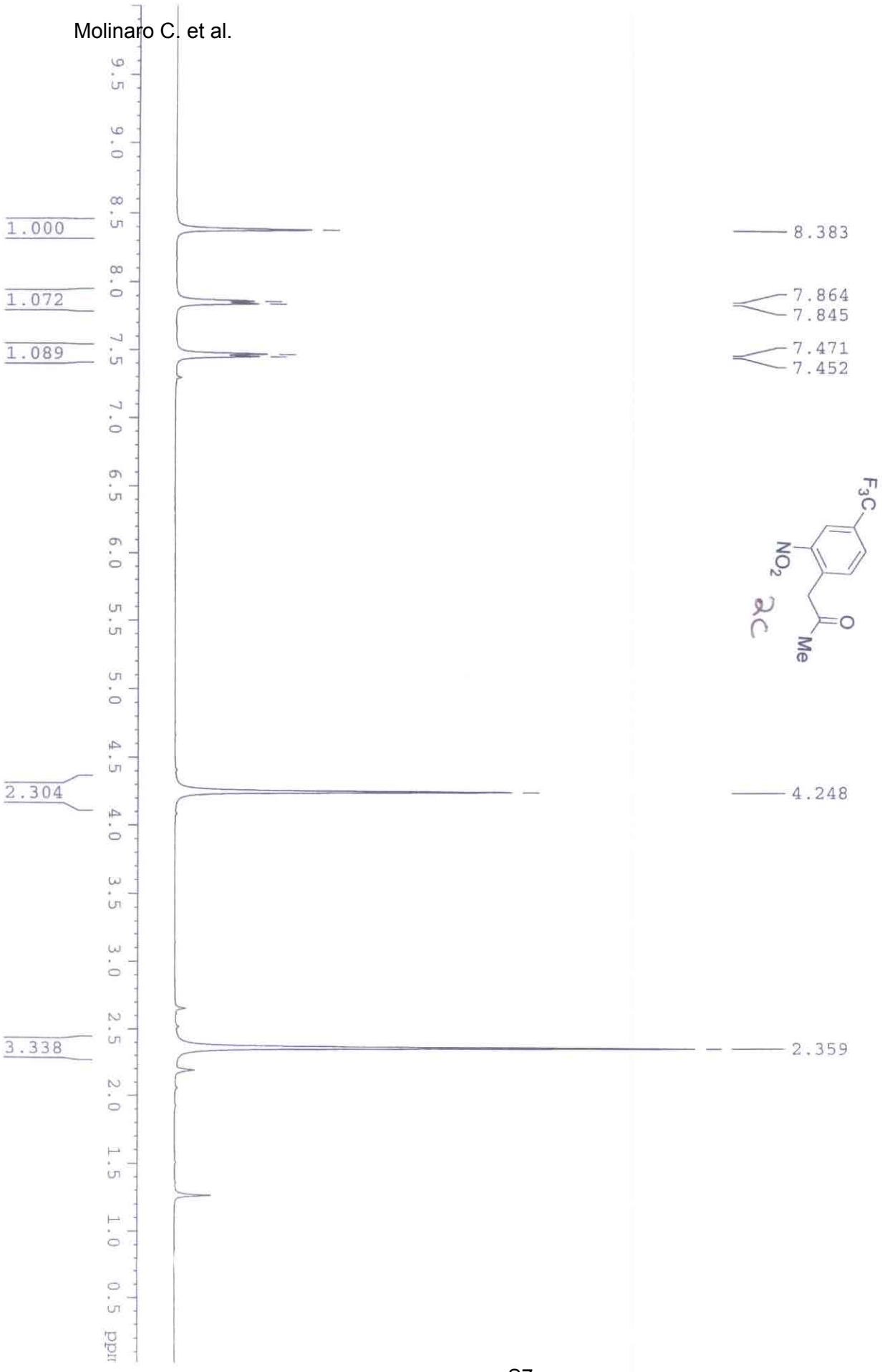
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2C
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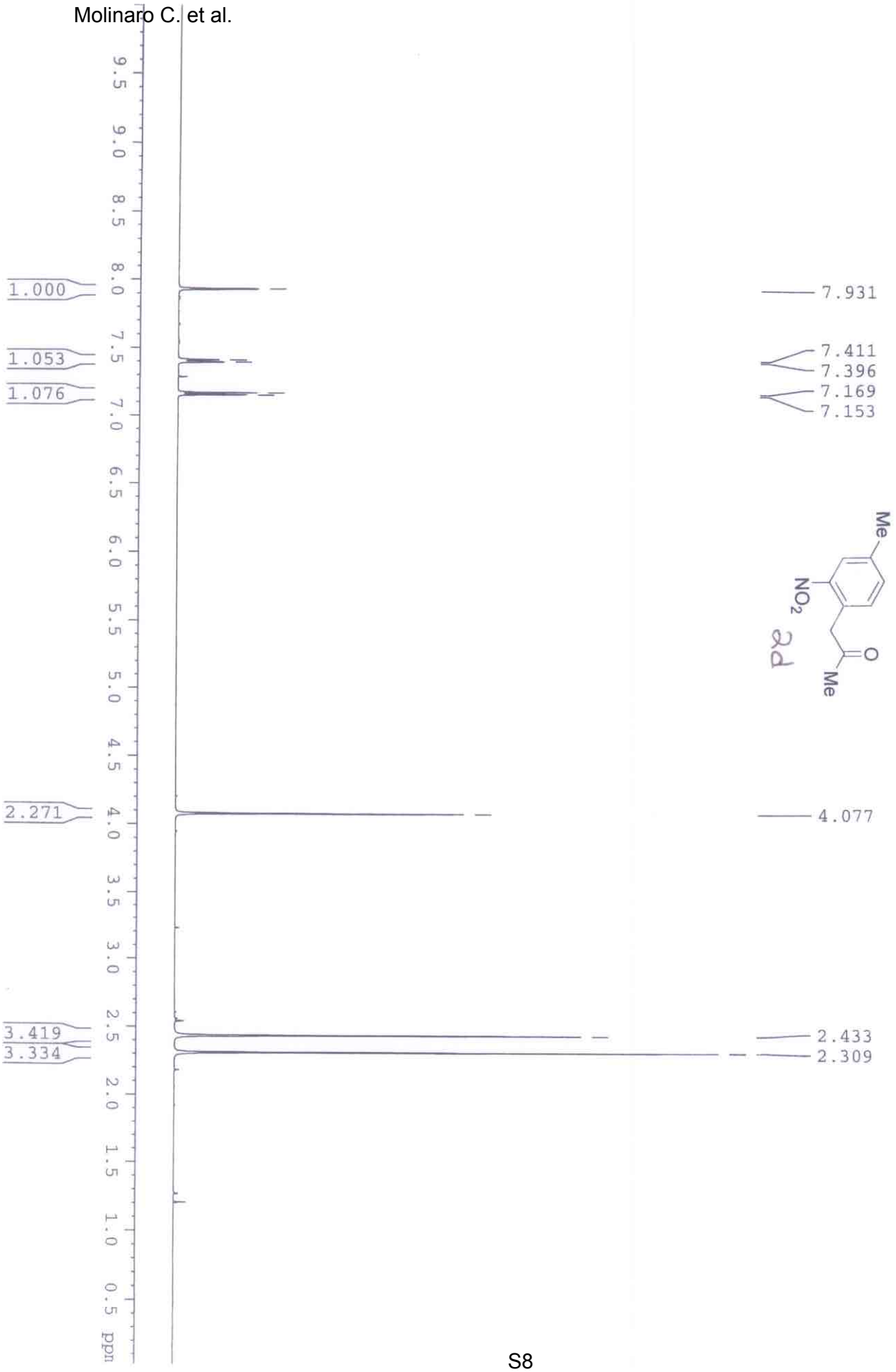
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O
Me
2d
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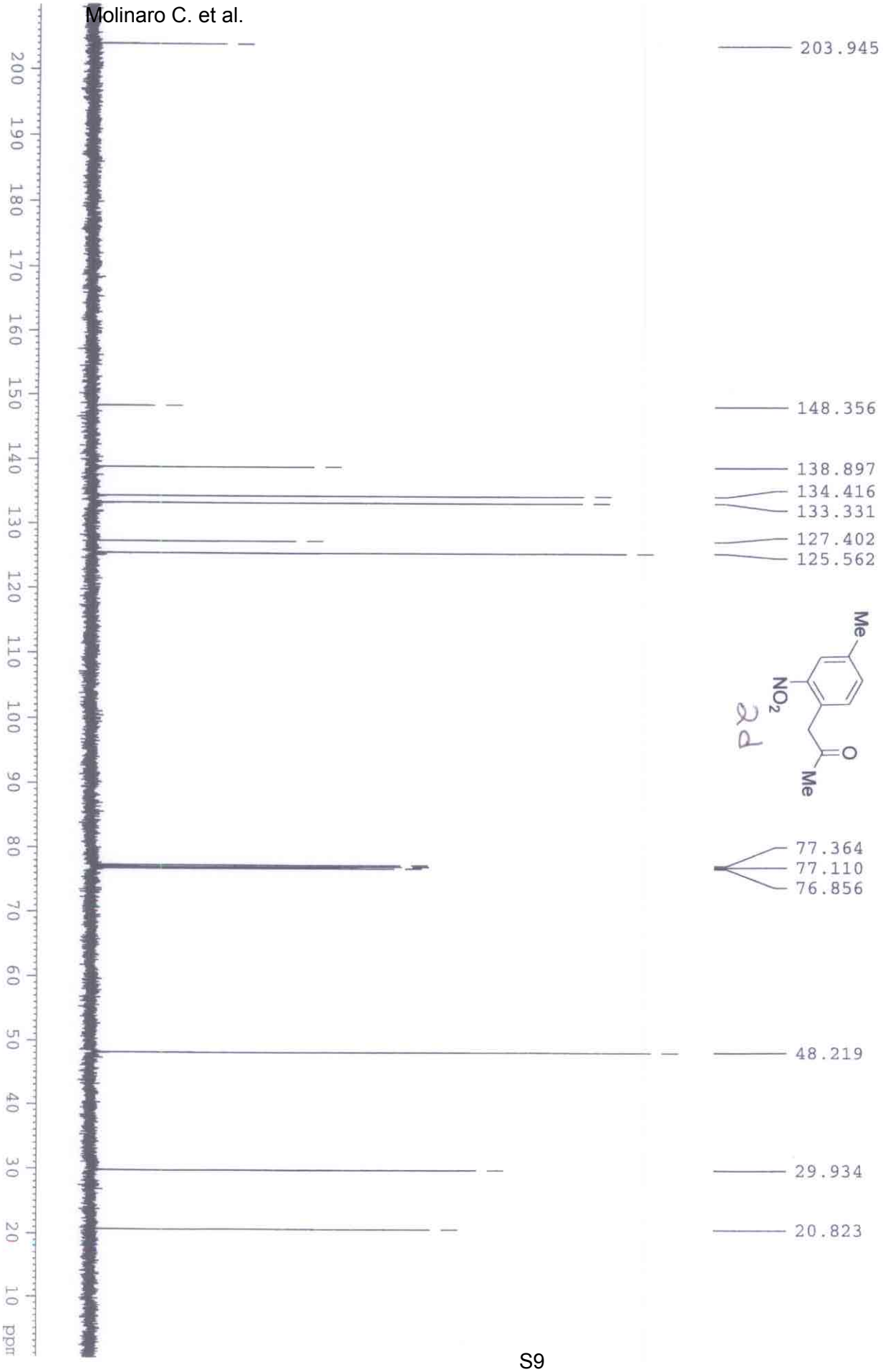
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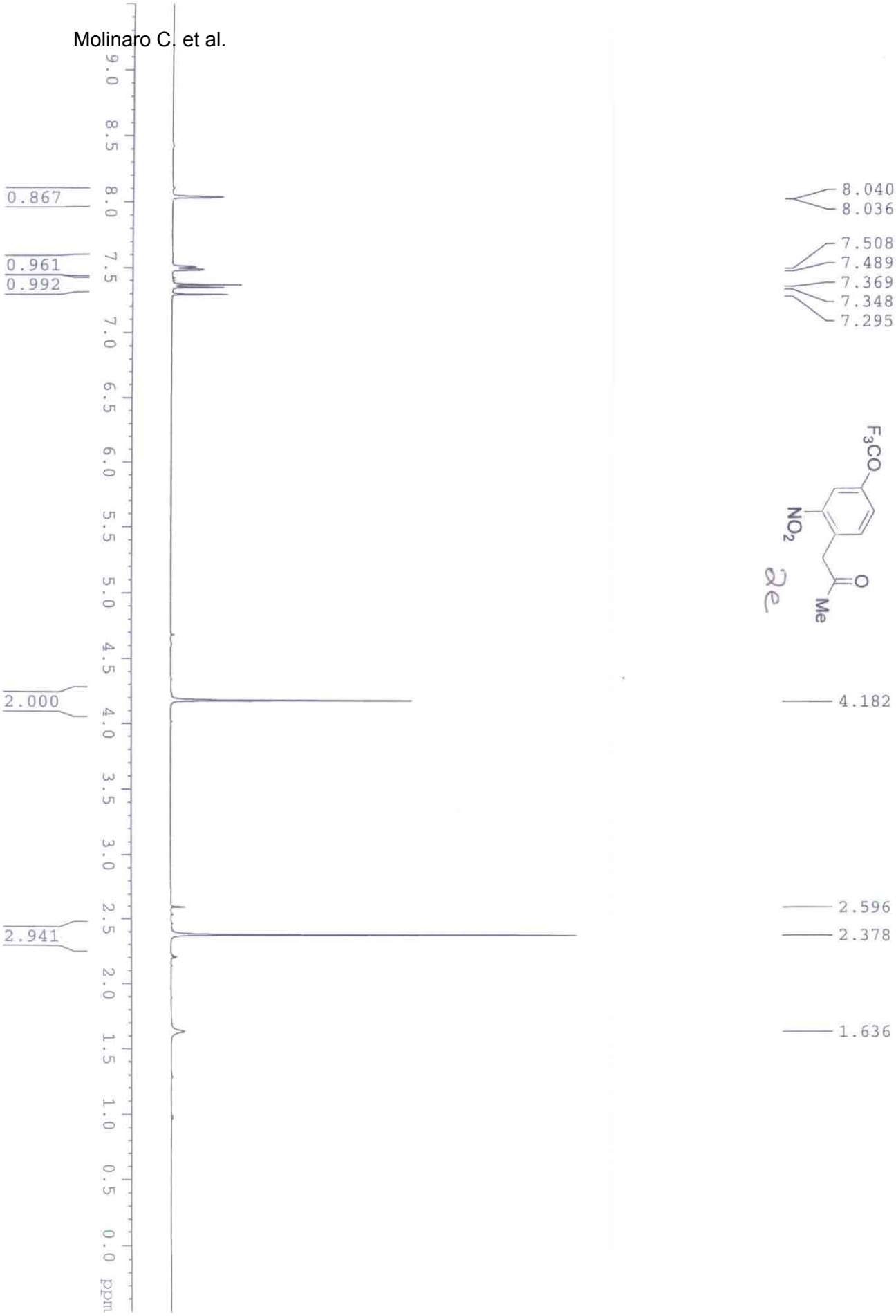
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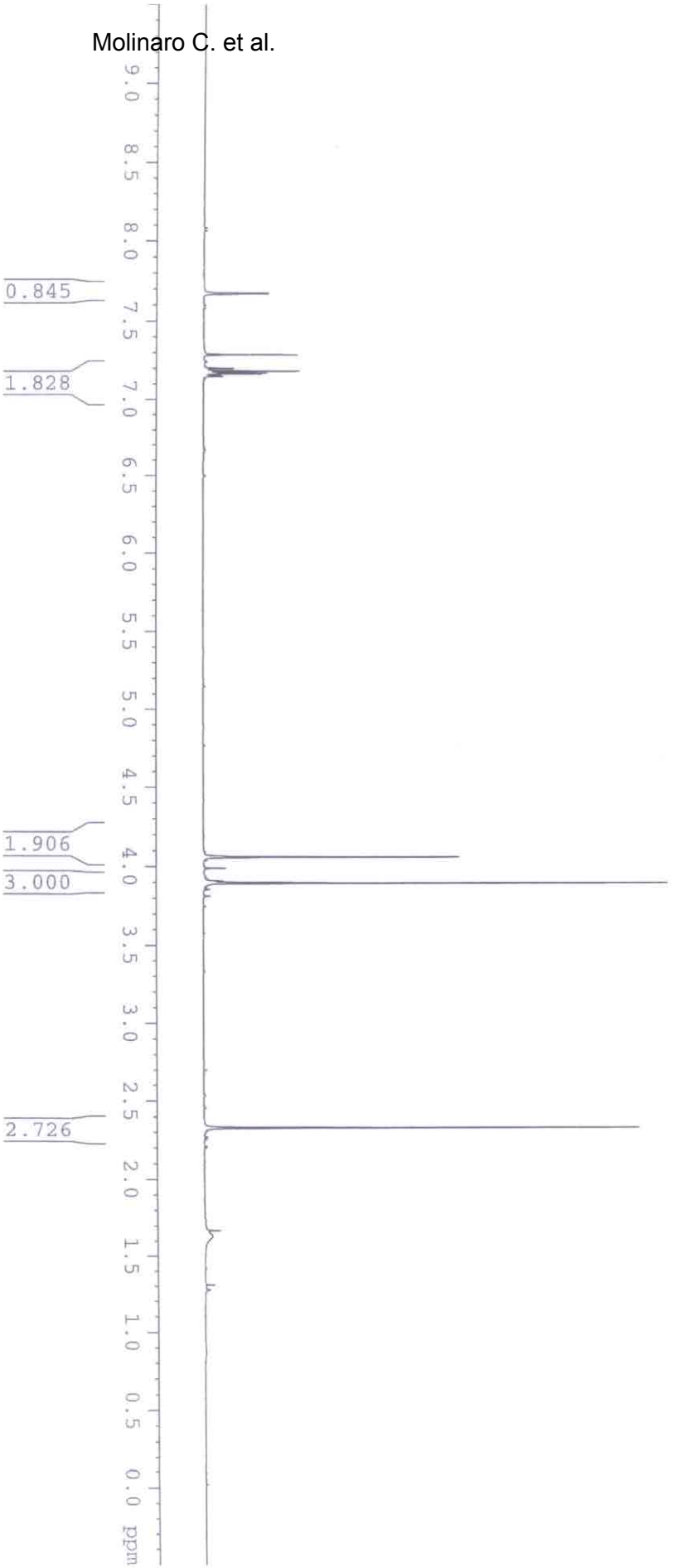
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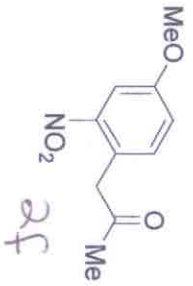
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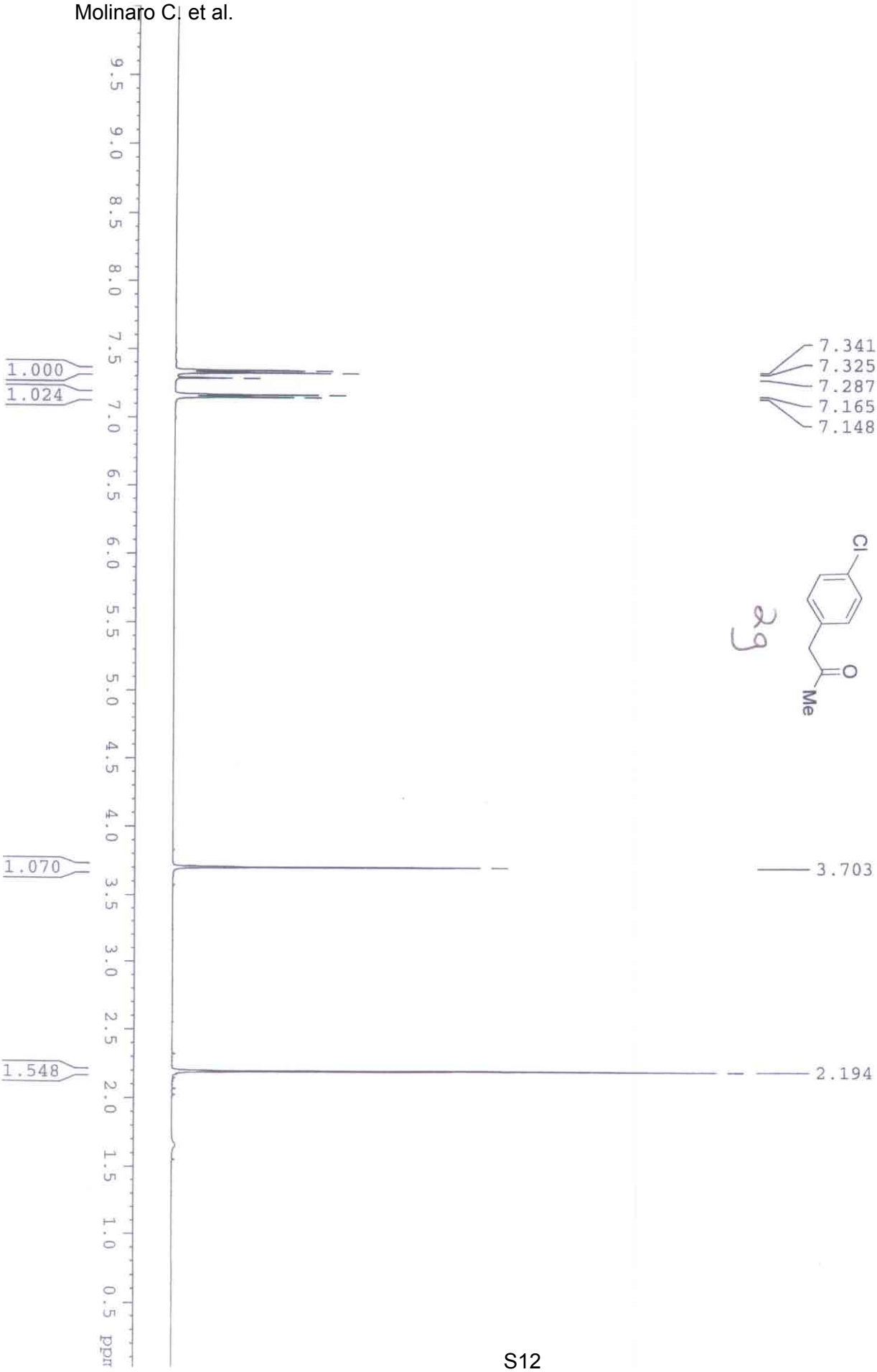
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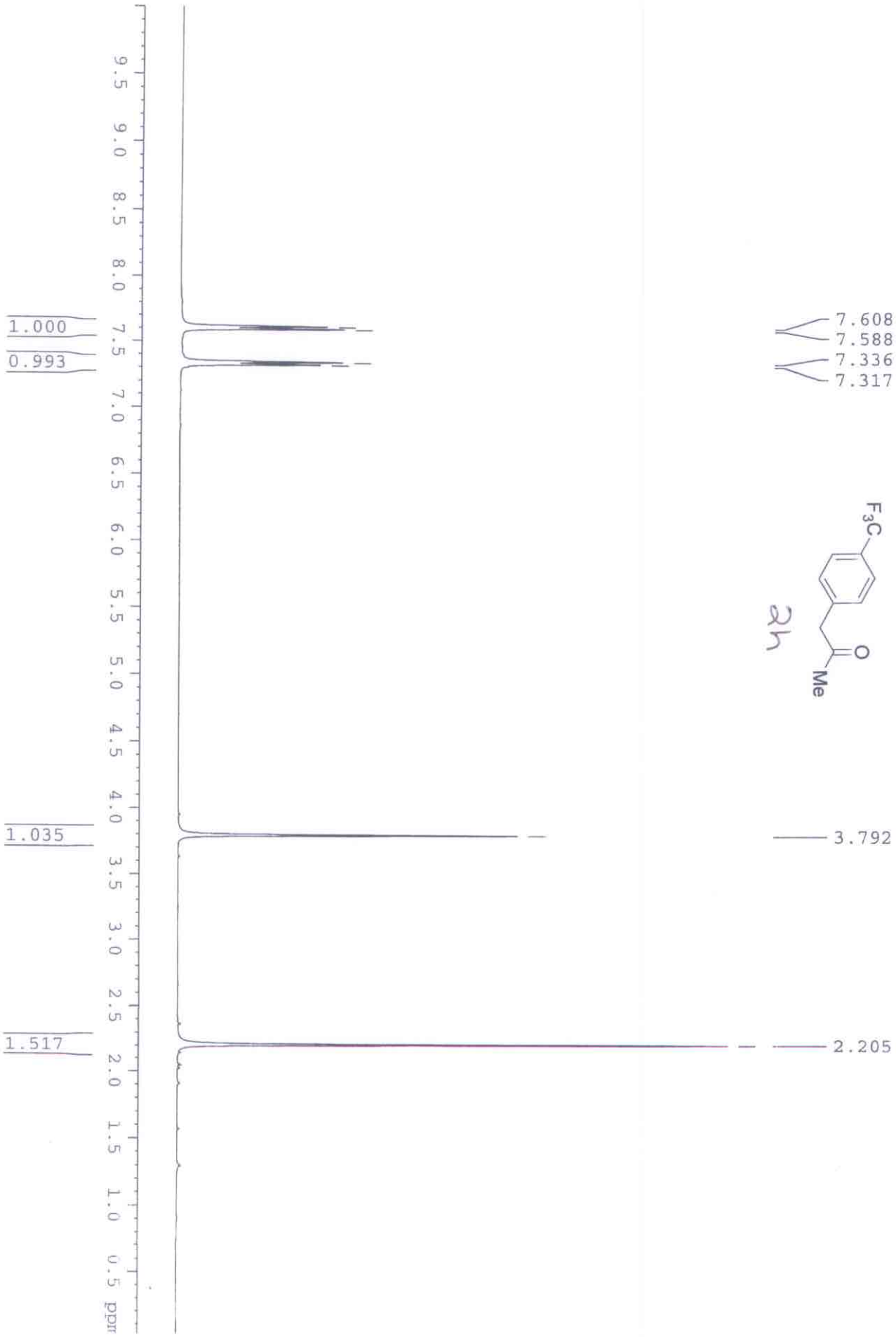
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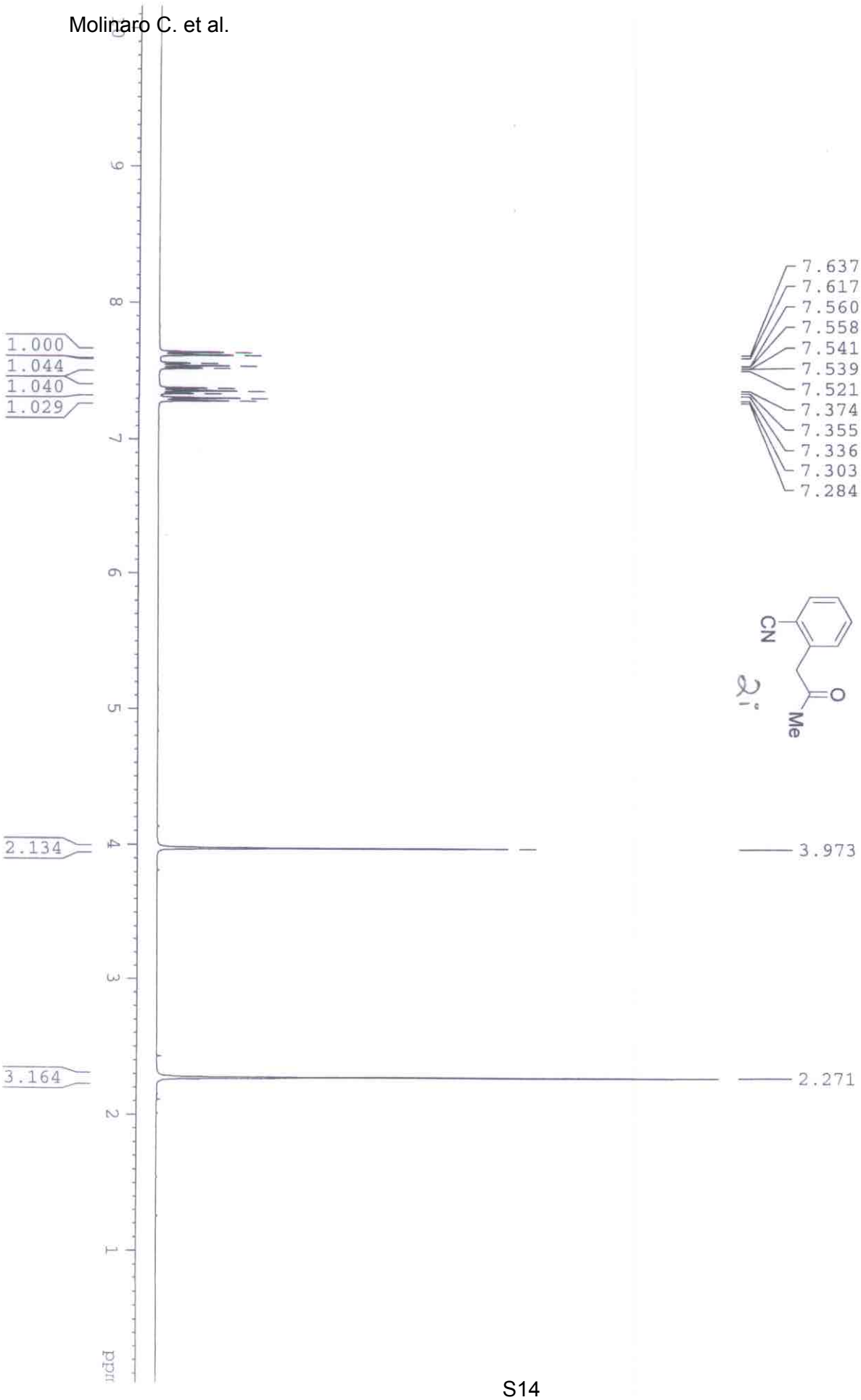
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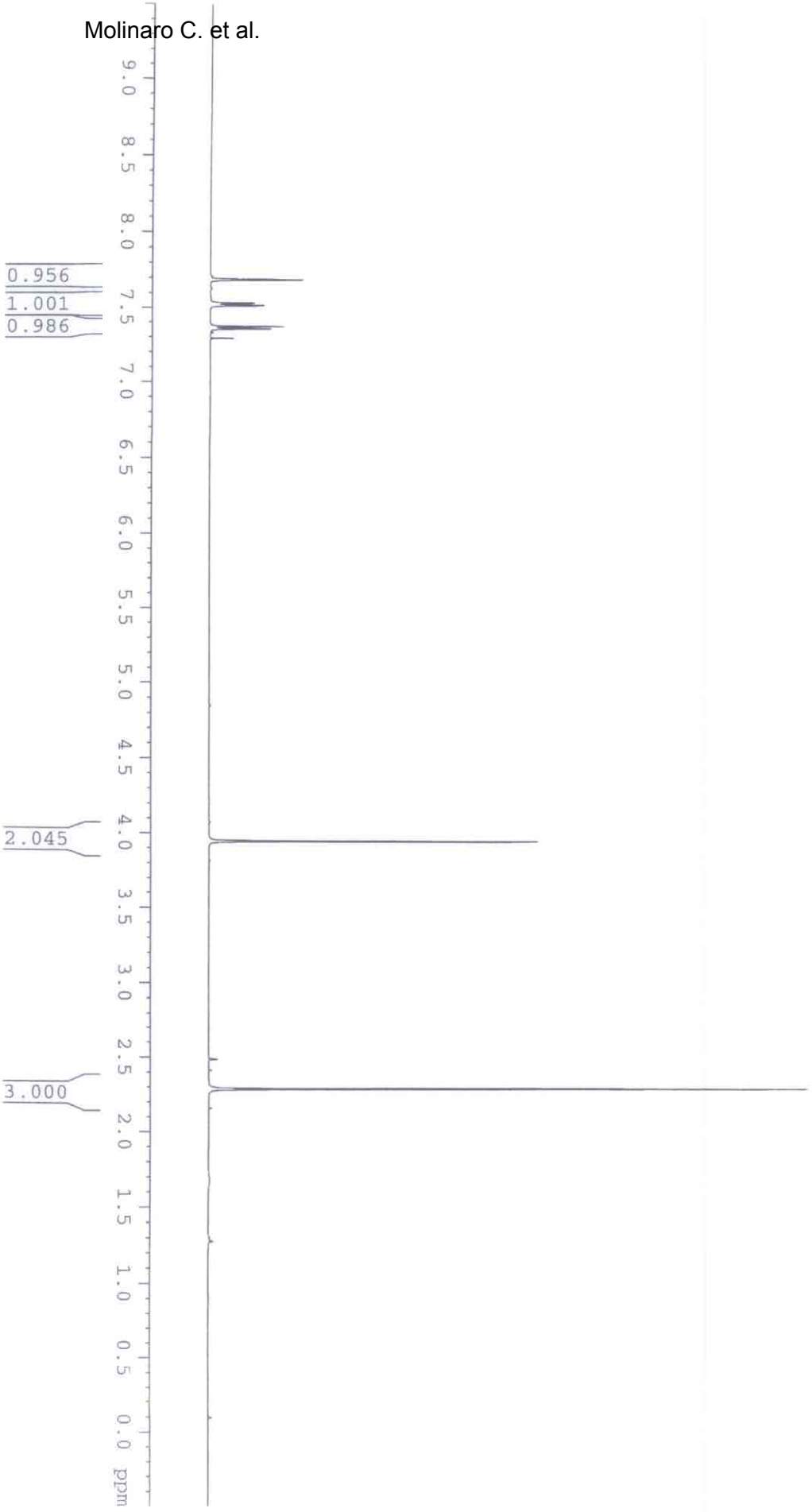
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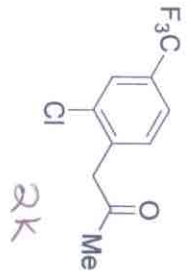
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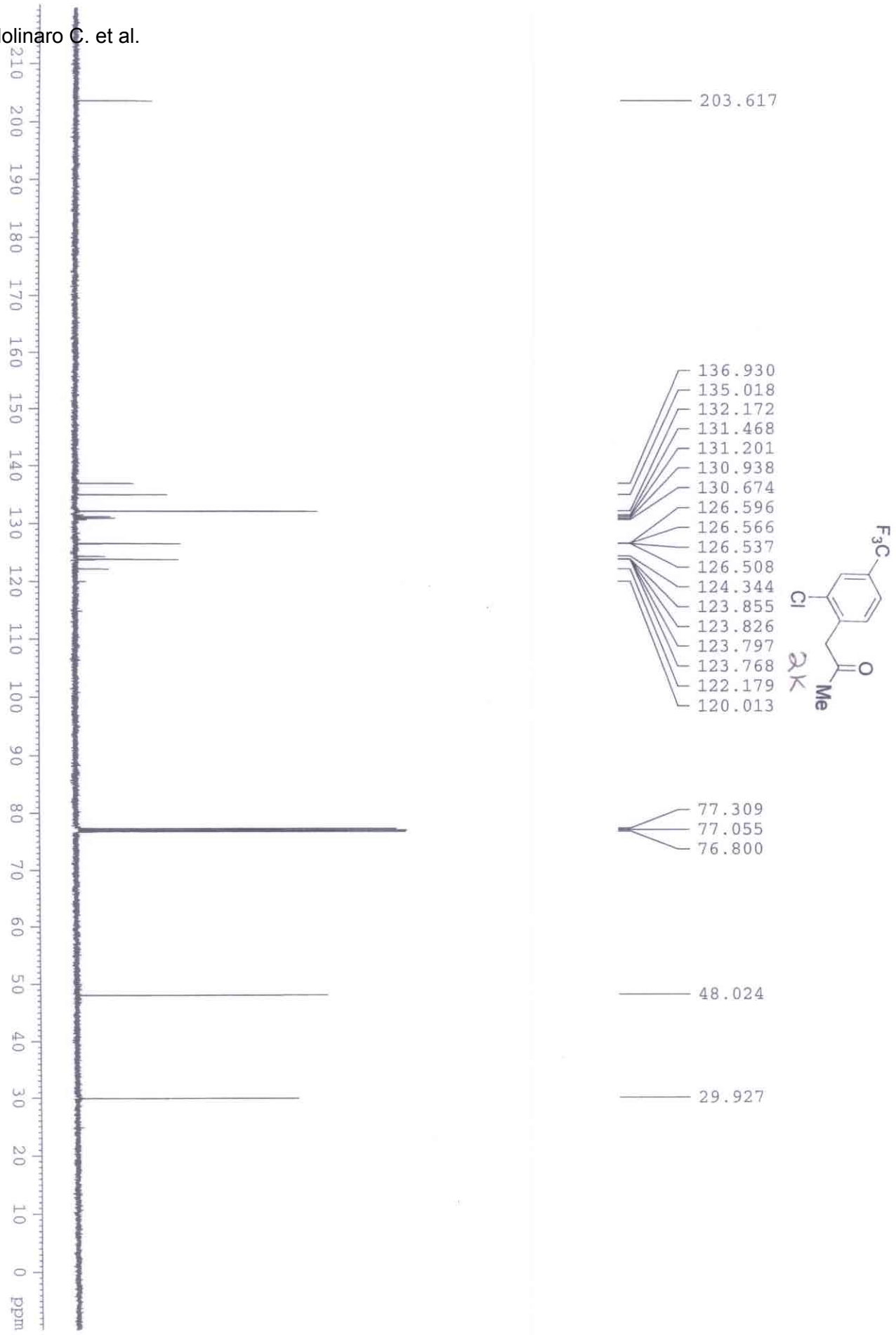
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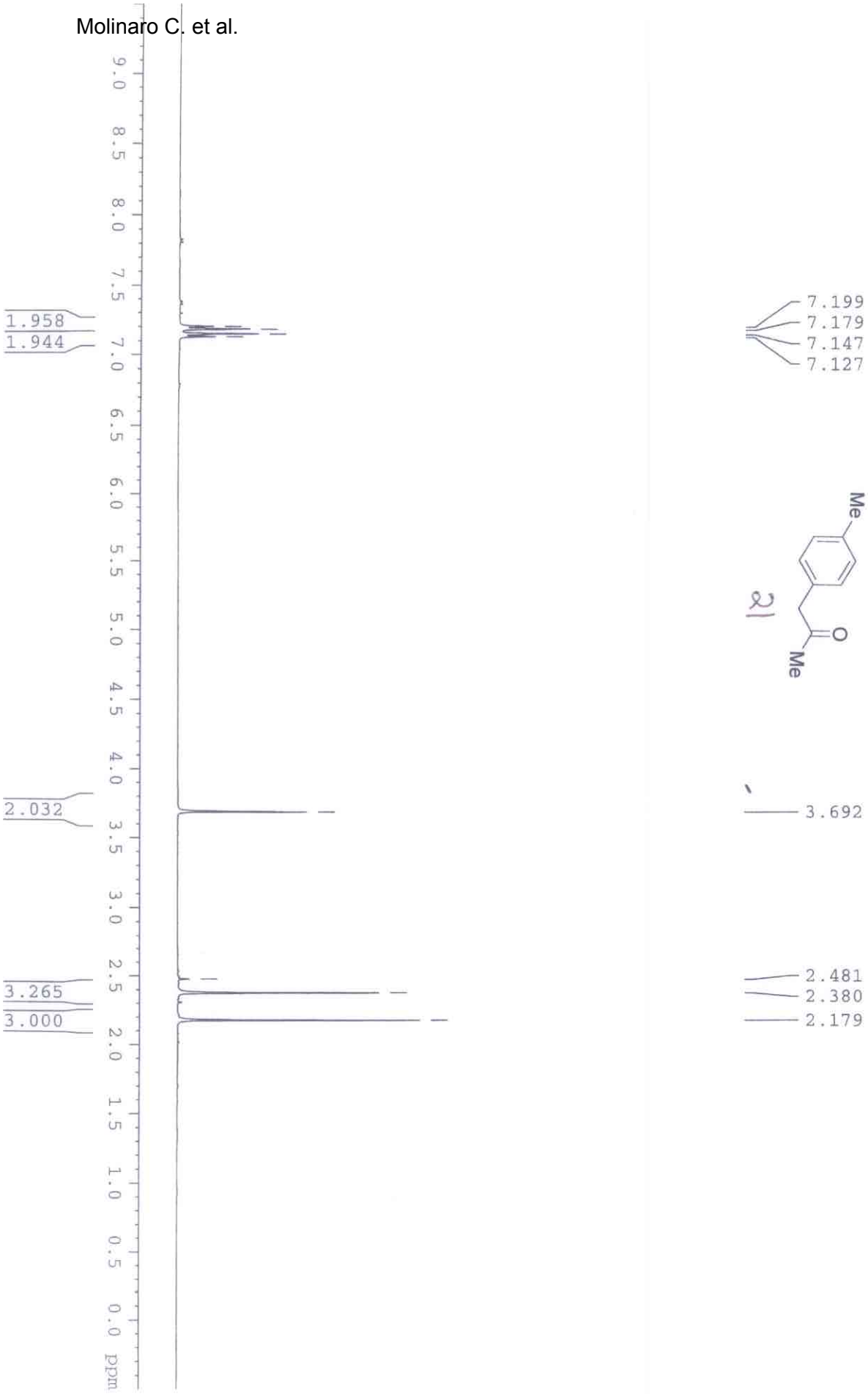
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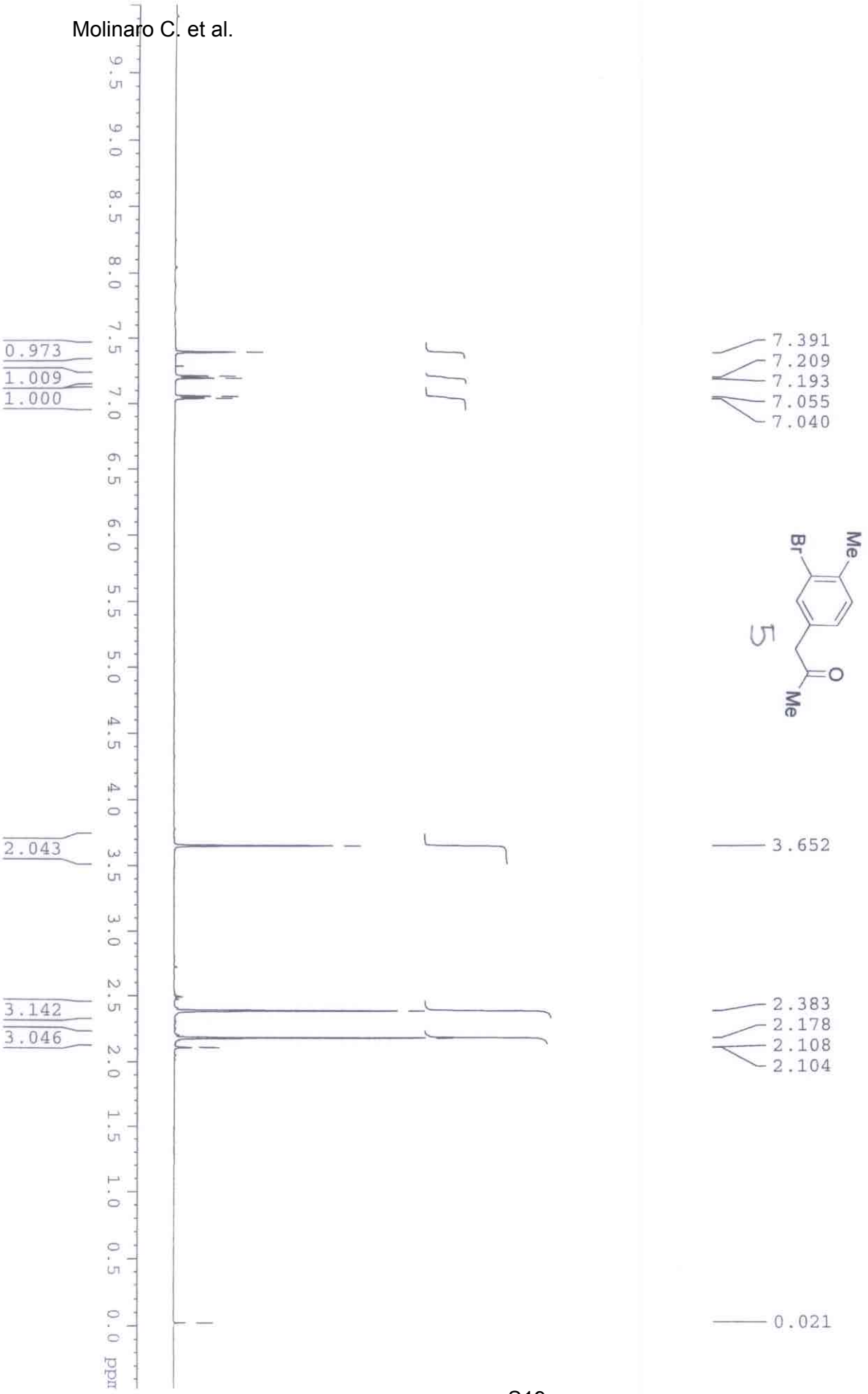
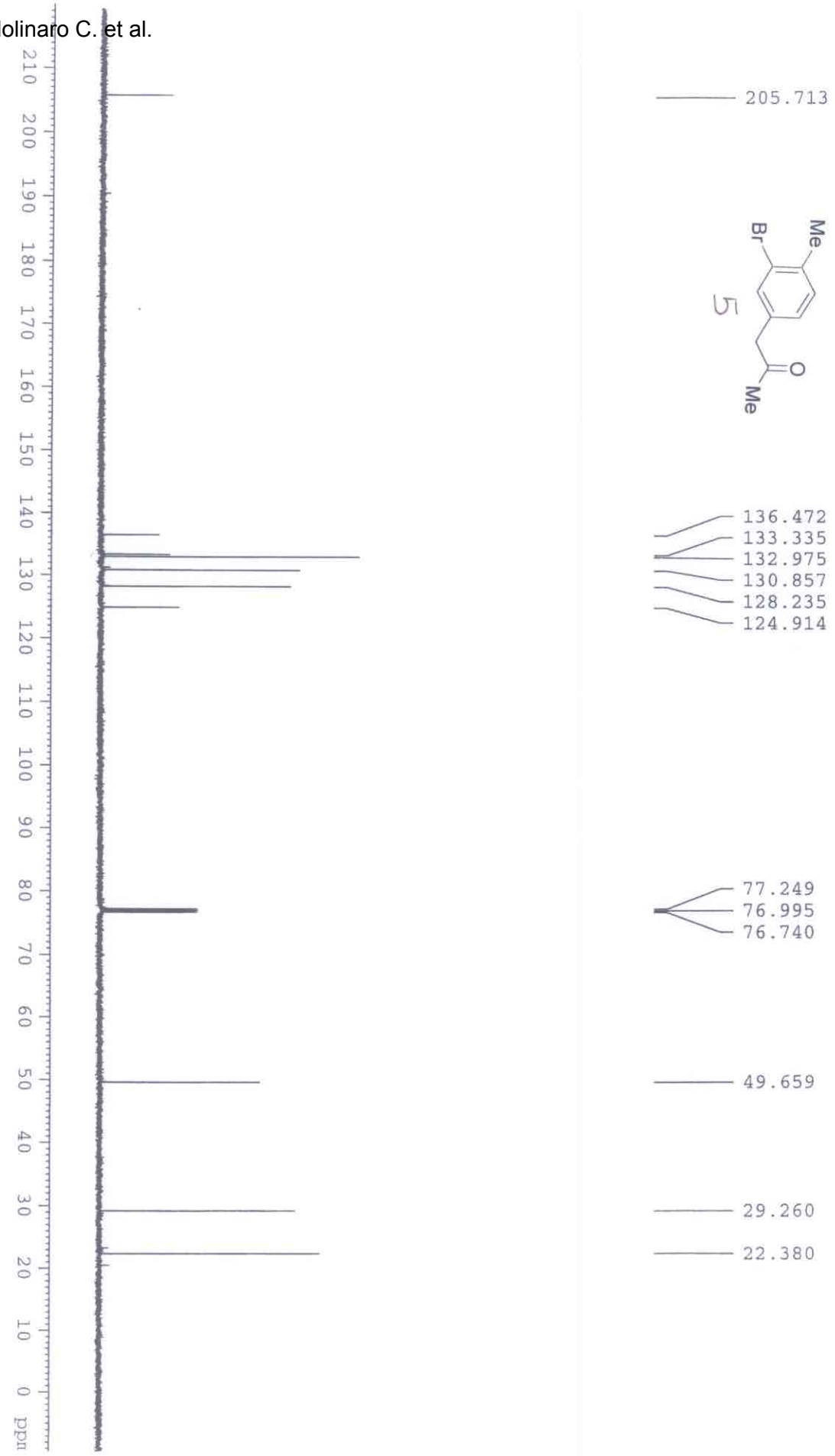
2.380
2.179


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.973
1.009
1.000
2.043
3.142
3.046
7.391
7.209
7.193
7.055
7.040
3.652
2.383
2.178
2.108
2.104
0.021
Br
Me
O
Me
5


205.713
Me
Br
5
O
Me
136.472
133.335
132.975
130.857
128.235
124.914
77.249
76.995
76.740
49.659
29.260
22.380
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm