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Full Paper

Synthesis of 1-Aryl-3-phenethylamino-1-propanone Hydrochlorides as Possible Potent Cytotoxic Agents

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Abstract: 1-Aryl-3-phenethylamino-1-propanone hydrochlorides **1-10**, which are potential potent cytotoxic agents, were synthesized via Mannich reactions using paraformaldehyde, phenethylamine hydrochloride as the amine component and acetophenone, 4'-methyl-, 4'-methoxy-, 4'-chloro-, 4'-fluoro-, 4'-bromo-, 2',4'-dichloro-, 4'-nitro-, 4'-hydroxyacetophenone or 2-acetylthiophene as the ketone component. Yields were in the 87-98 % range. Of the compounds synthesized, compounds **2**, **6-8** and **10** were new. The optimum reaction conditions were investigated by changing the mol ratios of the reactants, the solvents and the acidity levels using **1** and **10** as representative targets. It was observed that the best mol ratio of the ketone, paraformaldehyde and phenethylamine hydrochloride was 1:1.2:1 (compared with a 2:2.1 ratio), and the most suitable reaction medium was ethanol containing concentrated hydrochloric acid (compared with only ethanol or no solvent). This study may serve as a guide for the conditions of the reactions to synthesize compounds having similar chemical structures.

Keywords: Acetophenone, mono-Mannich base, prodrug, spectral analyses, synthesis.

Introduction

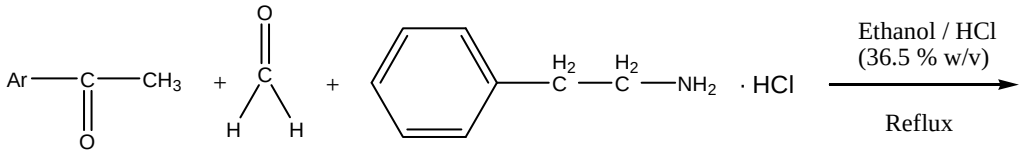
So-called Mannich bases are generally formed by the reaction between formaldehyde, a secondary amine and a compound containing reactive hydrogen atoms. On occasion, aldehydes other than formaldehyde may be employed and the secondary amine may be replaced by ammonia and primary amines. This process is known as the Mannich reaction [1]. Mannich bases display varied biological activities such as antimicrobial, cytotoxic, anticancer, analgesic, anti-inflammatory, diuretic and anticonvulsant properties [2-25]. The deamination process is important to evoke biological responses. Thus, an aminoketone possessing at least one activated hydrogen atom β to the amino group can undergo deamination *in vivo* or under simulated *in vitro* conditions to generate the corresponding α,β-unsaturated ketone. The biological activities of Mannich bases have been attributed to these liberated α,β-unsaturated ketones, which can alkylate nucleophiles, especially thiol groups [2, 5, 9, 10, 14, 26].

The key interests of our laboratory are the design, synthesis and evaluation of the biological activities of Mannich bases generally derived from acetophenones. We have previously reported the synthesis and diverse biological activities of some 3-amino-1-aryl-1-propanone hydrochloride mono-Mannich bases, in which the amine moiety was varied between dimethylamine, piperidine and morpholine, etc. [2, 4, 6-12, 14, 24-26]. Since we observed considerable biological activities in these compounds, we now aimed to design and synthesize some new 1-aryl-3-phenethylamino-1-propanone hydrochloride mono-Mannich bases, which are potential prodrugs of potent thiol-alkylating cytotoxic compounds.

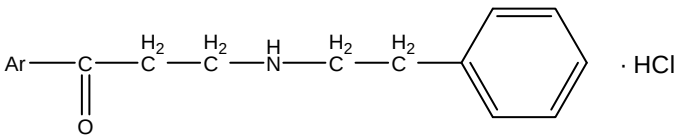
Results and Discussion

The synthetic route used for the preparation of the compounds **1-10** designed for this study is shown in Scheme 1.

Scheme 1. Synthetic pathway for the synthesis of the compounds **1-10**.



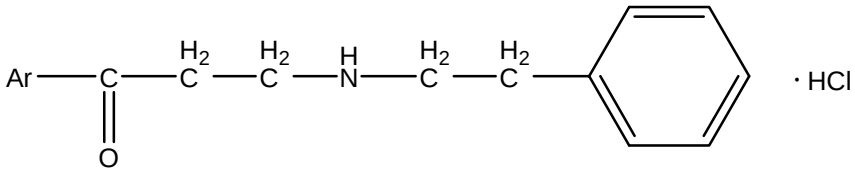
1 eq 1.2 eq 1 eq



The structures of the compounds thus prepared are shown in Figure 1. Of the compounds synthesized, compounds **2, 6-8,** and **10** were new, while compounds **1**, **3**-**5**, and **9** have been previously reported [16, 27-29]. The structures of the synthesized compounds were confirmed by ^{1}H- and ^{13}C-NMR (Table 1), UV, IR and MS data (Table 2). The purities of the compounds were confirmed by

elemental (C, H, N) analysis, which were within 0.4 % of the calculated values, with the sole exception of compound **9** (calculated: C: 66.77, H: 6.59, N: 4.58; found: C: 67.08, H: 6.36, N: 3.27).

Figure 1. Chemical structures of the synthesized compounds **1 -10**.



Ar: **1** = C_6H_5; **2** = 4'-$CH_3C_6H_4$; **3** = 4'-$CH_3OC_6H_4$; **4** = 4'-ClC_6H_4; **5** = 4'-FC_6H_4; **6** = 4'-BrC_6H_4; **7** = 2',4'-$(Cl)_2C_6H_3$); **8** = 4'-$NO_2C_6H_4$; **9** = 4'-HOC_6H_4; **10** = C_4H_3S(2-yl).

Table 1. ^{1}H- and ^{13}C-NMR spectra of the synthesized compounds **1-10**.

Compound	**^{1}H-NMR (DMSO-d_6)**	**^{13} C-NMR (DMSO-d_6)**
1	δ 2.96-3.17 (2H, m), 3.18-3.21 (2H, m), 3.28 (2H, t, *J* = 6.7 Hz), 3.55 (2H, t, *J* = 6.9 Hz), 7.22-7.34 (5H, m), 7.53-7.69 (3H, m), 7.96-7.98 (2H, m), 9.23 (1H, br s).	δ 32.2, 35.1, 42.4, 48.4, 127.4, 128.6, 129.31, 129.34, 129.5, 134.4, 136.5, 137.9, 197.6.
2	δ 2.37 (1H, s), 2.48-2.99 (2H, m), 3.18-3.37 (4H, m), 3.49 (2H, t, *J* = 6.9 Hz), 7.24-7.36 (7H, m), 7.87 (2H, d, *J* = 8.0 Hz), 9.10 (1H, br s).	δ 21.8, 32.2, 34.9, 42.5, 48.4, 127.4, 128.7, 129.3, 129.4, 130.0, 134.1, 137.9, 144.8, 197.1.
3	δ 2.96-3.00 (2H, m), 3.16-3.20 (2H, m), 3.26 (2H, t, J = 6.9 Hz), 3.47 (2H, t, *J* = 6.7 Hz), 3.83 (3H, s), 7.94 (2H, d, *J* = 8.7 Hz), 7.06 (2H, d, *J* = 8.7 Hz), 7.22-7.34 (5H, m), 9.16 (1H, br s).	δ 32.2, 34.7, 42.6, 48.4, 56.3, 114.7, 127.4, 129.31, 129.33, 129.5, 131.0, 137.9, 164.2, 195.9.
4	δ 2.94-2.99 (2H, m), 3.17-3.21 (2H, m), 3.28 (2H, t, *J* = 6.5 Hz), 3.52 (2H, t, *J* = 6.7 Hz), 7.22-7.34 (5H, m), 7.63 (2H, d, *J* = 8.4 Hz), 7.98 (2H, d, *J* = 8.7 Hz), 9.10 (1H, br s).	δ 32.2, 35.1, 42.3, 48.4, 127.4, 129.3, 129.4, 129.6, 130.6, 135.3, 137.9, 139.2, 196.7.
5	δ 2.95-2.99 (2H, m), 3.16-3.20 (2H, m), 3.27 (2H, t, *J* = 6.7 Hz), 3.53 (2H, t, *J* = 6.9 Hz), 7.21-7.41 (7H, m), 8.05 (2H, dd, *J* = 8.7, 5.4 Hz), 9.18 (1H, br s).	δ 32.2, 35.0, 42.4, 48.4, 116.5, 127.4, 129.3, 131.7, 133.3, 137.9, 164.7, 167.2, 196.2.
6	δ 2.95-3.00 (2H, m), 3.16-3.20 (2H, m), 3.27 (2H, t, *J* = 6.6 Hz), 3.52 (2H, t, *J* = 6.8 Hz), 7.22-7.34 (5H, m), 7.76 (2H, d, *J* = 8.4 Hz), 7.90 (2H, d, *J* = 8.4 Hz), 9.20 (1H, br s).	δ 32.2, 35.1, 42.3, 48.4, 127.4, 128.4, 129.31, 129.34, 130.6, 132.6, 135.6, 137.9, 196.9.
7	δ 2.96-3.00 (2H, m), 3.14-3.18 (2H, m), 3.26 (2H, t, *J* = 6.7 Hz), 3.50 (2H, t, *J* = 6.9 Hz), 7.20-7.33 (5H, m), 7.58 (1H, dd, *J* = 8.4, 2.4 Hz), 7.73 (1H, d, *J* = 2.2 Hz), 7.82 (1H, d, *J* = 8.4 Hz), 9.20 (1H, br s).	δ 32.2, 38.9, 42.1, 48.4, 127.4, 128.4, 129.30, 129.31, 130.9, 132.01, 132.05, 136.5, 137.4, 137.9, 198.4.
8	δ 3.12-3.16 (2H, m), 3.37-3.45 (2H, m), 3.57-3.61 (2H, m), 3.80 (2H, t, *J* = 6.7 Hz), 7.22-7.35 (5H, m), 8.24 (2H, d, *J* = 8.7 Hz), 8.37 (2H, d, *J* = 9.1 Hz), 11.09 (1H, br s).	δ 30.0, 33.8, 47.8, 54.3, 124.5, 127.4, 129.2, 129.5, 130.1, 137.7, 141.3, 150.8, 196.6.

Table 1. Cont.

9	δ 3.08-3.58 (8H, m), 6.88 (2H, d, *J* = 8.7 Hz), 7.21-7.34 (5H, m), 7.89 (2H, d, *J* = 8.7 Hz), 10.57(1H, s), 10.60 (1H, br s).	δ 30.0, 32.5, 48.3, 54.2, 115.9, 127.4, 128.3, 129.2, 129.5, 131.3, 137.7, 163.2, 195.4.
10	δ 2.95-2.99 (2H, m), 3.14-3.18 (2H, m), 3.26 (2H, t, *J* = 6.9 Hz), 3.48 (2H, t, *J* = 6.9 Hz), 7.22-7.34 (5H, m), 7.98 (2H, dd, *J* = 4.0, 1.1 Hz), 8.05 (2H, dd, *J* = 4.7, 1.1 Hz), 9.20 (1H, br s).	δ 32.2, 35.4, 42.3, 48.4, 127.4, 129.31, 129.33, 129.6, 134.5, 136.1, 137.9, 143.4, 190.5.

Table 2. UV, IR and MS results for the synthesized compounds.

Compound	**MW**	**UV***			**MS m/z M^+**	**IR (KBr, cm^{-1})**
		λ_{max}	**logε**	**C(M)**		**C=O stretching**
1	289.80	244	4.12	$5.1x10^{-5}$	253.3	1678
2	303.83	255	4.2	$6.58x10^{-5}$	267.7	1677
3	319.83	286	3.81	$12.5x10^{-5}$	283.4	1655
4	324.24	253	4.21	$3.8x10^{-5}$	287.7	1675
5	307.79	245	4.03	$6.5x10^{-5}$	271.6	1671
6	368.70	258	4.28	$5.4x10^{-5}$	331.0	1672
7	427.58	248	3.85	$13.9x10^{-5}$	321.3	1701
8	334.80	262	4.33	$4.48x10^{-5}$	298.5	1695
9	305.80	283	4.48	$3.2x10^{-5}$	269.3	1666
10	295.83	262, 287	3.95, 3.86	$13.5x10^{-5}$	259.4	1651

*Except for compound **8**, all UV spectra were recorded in ethanol.

Product characterization

The characterization of compound **1** is presented in some detail as a representative example. In the ^{1}H-NMR spectrum of compound **1** (Table 1), the protons of the two methylene groups located on each side of the nitrogen atom were observed as multiplets (2 x 2 H) at δ 2.96-3.17 and 3.18-3.21 ppm, while the two protons of the methylene located next to the phenyl ring were observed as a triplet at δ 3.28 ppm (*J* = 6.7 Hz) and the two protons of the methylene located next to the carbonyl group were observed as a triplet at δ 3.55 ppm (*J* = 6.9 Hz). The phenyl ring aromatic protons were observed as multiplets at δ 7.22-7.34 ppm (5 H), δ 7.53-7.69 ppm (3 H) and δ 7.96-7.98 ppm (2 H). A broad singlet at δ 9.23 ppm (1 H) suggested an NH proton, in accordance with the proposed chemical structure. In the ^{13}C-NMR spectrum of compound **1** (Table 1), methylene carbons at δ 32.2, 35.1, 42.4 and 48.4 ppm, aromatic carbons at δ 127.4, 128.6, 129.31, 129.34, 129.5, 134.4, 136.5 and 137.9 ppm and a carbonyl carbon at δ 197.6 ppm were observed, all in agreement with the proposed structure. In the IR spectrum of compound **1** (Table 2) a strong absorption peak at 1678 $cm^{-1}$was observed, also suggesting the presence of a carbonyl group. The UV spectrum of compound **1,** taken in ethanol (Table 2), gave a

λ_{max} peak at 244 nm, also in agreement with the proposed structure. The mass spectrum of compound **1** (Table 2) gave a signal at 253.3, which corresponds to the m/z value of the basic form of compound **1**, thus confirming the chemical structure of **1**.

Synthetic condition optimization

Using compounds **1** and **10** as representative compounds, different reaction conditions were tested to optimize the synthetic conditions for the whole series. These experiments are summarized in Table 3.

Table 3. Optimization of reaction conditions.

Entry	Target compound	Reagent ratio[a]	Solvent	Acid	Time	Yield (%)
A	**1**	1:1.2:1	Ethanol	Yes	7 hrs	95
B	**10**	1:1.2:1	Ethanol	Yes	7 hrs	93
C	**1**	1:1.2:1	Ethanol	No	13 hrs	95
D	**10**	1:1.2:1	Ethanol	No	19 hrs	96
E	**1**	2:2:1	Ethanol	Yes	8 hrs	74
F	**10**	2:2:1	Ethanol	Yes	14 hrs	69
G	**1**	2:2:1	Ethanol	No	7 hrs	0
H	**10**	2:2:1	Ethanol	No	16 hrs	74
I	**1**	2:2:1	None	No	– [b]	18[c]
J	**10**	2:2:1	None	No	– [b]	16[d]
K	**1**	1:1.2:1	None	No	– [b]	37
L	**10**	1:1.2:1	None	No	– [b]	47

[a] Ketone:paraformaldehyde:phenethylamine hydrochloride

[b] Reaction mixture heated to 83-86˚C (ca. 10 minutes); then an exothermic reaction ocurred (see text for details)

[c] 15 % of 1-phenethyl-3-benzoyl-4-phenyl-4-piperidinol was also formed

[d] 21 % of 1-phenethyl-3-(2-thienylcarbonyl)-4-(2-thienyl)-4-piperidinol was also formed

When the syntheses of these two compounds were carried out under the reaction conditions described in the Experimental, i.e. by refluxing a 1:1.2:1 mixture of ketone (acetophenone for **1** and 2-acetylthiophene for **10**), paraformaldehyde and phenethylamine hydrochloride in ethanol which was acidified with hydrochloric acid, compounds **1** and **10** were obtained in yields of 95% and 93%, respectively (Table 3, entries A, B). On the other hand, when compounds **1** and **10** were prepared by refluxing the reactants in the same 1:1.2:1 mol ratio in ethanol *without* acid (entries C, D), compound **1** was still obtained in 95% yield, while compound **10** was obtained in slightly better yield (96%). Although the yields of compounds **1** and **10** were therefore essentially unchanged in the presence or absence of acid, in order to obtain these similar yields under the latter conditions the reflux periods had to be extended by six hours for **1** (almost twice as long) and 12 hours (almost three times as long) for **10**. From this it may be concluded that the acidic medium helps to decrease the reaction period by increasing the reaction rate.

When compounds **1** and **10** were prepared in ethanol acidified with concentrated hydrochloric acid but using the appropriate ketone, paraformaldehyde and phenethylamine hydrochloride in a 2:2:1 mol ratio, the reflux periods were eight hours for **1** and 14 hours for **10** and the yields of the reactions were 74 and 69%, respectively (entries E, F), that is, compared with the reactions in the same reaction medium in which the mol ratio of the reactants was 1:1.2:1 (entries A, B), the reaction yields decreased by 21% for compound **1**, while reaction period was almost the same, while the yield of compound **10** decreased 24 %, while the reaction period increased two-fold. These results suggested that the best results in terms of reaction yields and especially the reaction time could be achieved by carrying out the reactions in refluxing ethanol acidified with concentrated hydrochloric acid and using of a 1:1.2:1 mol ratio of ketone, paraformaldehyde and phenethylamine hydrochloride.

Compound **1** could not be synthesized when the reactions were run in ethanol *without* acid using a 2:2:1 mol ratio of reagents, even when the reaction mixture was refluxed for seven hours (entry G). Under these conditions, formation of compound **10** only started after two hours and its production reached its maximum after 16 hours, at which time the reaction was stopped and compound **10** was isolated in 74 % yield (entry H). When these results are compared with those obtained using the same 2:2:1 mol ratio of the reactants but in an acidic ethanolic reaction medium (entries E, F), it is noted that the acidity of the reaction medium seems to be crucial for the synthesis of compound **1**, whereas in the case of compound **10**, although the reaction time was slightly longer, the yield of the reaction increased by only 5%. When the representative compounds **1** and **10** were synthesized by heating the reactants in 2:2:1 mol ratio in an oil bath in the absence of any solvent and acid (entries I, J), an exothermic reaction was observed after approximately 10 minutes, when the reaction mixture reached a temperature of 83-86 ^{o}C, and the products melted giving a homogeneous mixture. Even if the heat source was removed at this point, the exotherms reached 100 ˚C (entry I) and 108 ˚C (entry J). When the reaction mixtures had cooled sufficiently ethyl acetate was added and stirring was continued for 17 hrs, to give **1** and **10** in 18 % and 16 % yield, respectively. Under these conditions additional reaction products were also obtained (1-phenethyl-3-benzoyl-4-phenyl-4-piperidinol in addition to compound **1** and 1-phenethyl-3-(2-thienylcarbonyl)-4-(2-thienyl)-4-piperidinol in addition to compound **10**, in yields of 15 and 21%, respectively). The production of these piperidinol type byproducts in addition to the desired compounds **1** and **10** was the main difference of this method from the others tried. Comparing the yields of the reactions in which a 2:2:1 mol ratio of reagents was used but without solvent (entries I, J) with the yields using the same ratio of the reactants in acidified ethanol (entries E, F), it is observed that the yield of compound **1** in acidified ethanol (74%) decreased to 18% without solvent, and similarly, the yield of compound **10** decreased from 69% to 16%. When the yields of the reactions without solvent and the reactants in 2:2:1 mol ratio (entries I, J) are compared with the corresponding yields of the reactions with the same ratio of the reactants in ethanol without acid (entries G, H), it was observed that reaction yield in ethanol medium (0%) increased to 18% for compound **1** in a medium without solvent. In case of compound **10**, the reaction yield with the ethanol medium (74%) decreased to 16% in a medium without solvent. On the other hand, when the reaction conditions without solvent and a 2:2:1 mol ratio of reactants (entries I, J) are compared with the conditions without solvent but with a 1:1.2:1 mol ratio of reactants (entries K, L), the yields improved from 18% to 37% for **1** and from 16% to 47% for **10** under the latter conditions, as piperidinol byproduct formation is no longer possible with this stoichiometry.

The ratios of ketone, paraformaldehyde amine HCl previously used [16] in the preparation of compound **3** were 1:1.7:1.5, and the paraformaldehyde was added in two portions, which differs from our method. The medium was acidified with HCl after heating for 7 h. First the basic form of compound **3** was obtained using 50% NaOH, and then compound **3** itself was obtained by passing gaseous HCl through a solution of the base in ether. The yield was 64% after purification by crystallization. The reason for a lower yield than that obtained by our method (94%) could be the formation of byproducts such as α,β-unsaturated ketone and piperidinol type compounds, due to deamination of compound **3** in the NaOH solution used [10, 13]. In the preparation of compounds **4** and **5** the ratios of ketone, paraformaldehyde and amine HCl previously used were 1:1.7:1 and the reaction mixtures were heated in acidic isopropanol [28]. The compounds were purified by crystallization and obtained in yields of 35% to 40%, respectively. The difference in the reaction solvent (isopropanol vs. ethanol used in our study) might have affected the yield of the reaction.

Conclusions

In conclusion, the syntheses in high reaction yields between 87-98 % and the spectral data of the compounds **1- 10,** which are potential bioactive compounds, are reported for the first time in detail. Of these compounds, **2, 6-8,** and **10** are new. The optimum reaction conditions for the synthesis of the 1-aryl-3-phenethylamino-1-propanone hydrochloride mono Mannich bases reported in this study were investigated by changing the mol ratios of reactants, solvent and acidity level, using **1** and **10** as representative compounds, It was observed that the most suitable mol ratio of ketone, paraformaldehyde and phenethylamine hydrochloride reactants was 1:1.2:1 (compared with 2:2.1) and the most suitable reaction medium was ethanol containing concentrated hydrochloric acid (compared with the reaction without solvent and using only ethanol). This study may serve as a guide for the synthesis conditions of the compounds with similar chemical structures.

Experimental

General

Chemicals used in this study were as follows: acetophenone, 4’-hydroxyacetophenone (Merck, Hohenbrunn, Germany), 4’-methylacetophenone, 4’-nitroacetophenone, 4’-chloroacetophenone, 2-acetylthiophene (Fluka, Steinheim, Switzerland), 4’-methoxyacetophenone, 4’-fluoroacetophenone, 4’-bromoacetophenone, 2’,4’-dichloroacetophenone (Acros, Geel, Belgium), paraformaldehyde (Merck, Darmstadt, Deutschland), methanol, ethyl acetate (Riedel-deHaën, Seelze, Germany) and ethanol (J.T. Baker, Deventer, Holland). The ^{1}H- and ^{13}C-NMR spectra were recorded at 400 (100) MHz on a Varian spectrometer (Danbury, USA). Infrared spectra were obtained for KBr disks on a Mattson 1000 FT-IR spectrophotometer (Cambrige, England). Elemental analyses were carried out with a Leco CHNS-932 instrument (Michigan, USA). EI-MS spectra were recorded on a Thermo-Finnigan mass analyzer (San Jose, USA). UV spectra of compounds were recorded on a Thermo Electron Heλios (α) (UVA 114903) spectrometer (Cambridge, UK). Melting points were measured with an Electrothermal IA 9100 (Essex, UK).

Synthesis of 1-aryl-3-phenethylamino-1-propanone hydrochlorides **1-10**

A previously reported Mannich reaction procedure [8, 10] was followed. The appropriate ketone, paraformaldehyde and phenethylamine hydrochloride in 1:1.2:1 mol ratio were placed in a reaction flask containing ethanol (5 mL), then HCl (0.5 mL, 36.5 %, w/v) in ethanol (2 mL) was added to this mixture, which was then refluxed for varying periods of time. The reactions were followed by TLC analysis (Merck Art No. 5715: Silica gel 60 F_{254}, 0.25 mm thickness) with 4:1 $CHCl_3$:methanol as eluent and visualization with a UV lamp. Refluxing was continued until the ketone component of the reaction mixture was consumed. The amounts (mmol) of ketone, paraformaldehyde and phenethylamine hydrochloride used, reflux times (hours), crystallisation solvents used, yields of the reactions (%) and melting points of the products (^oC) are summarized in Table 4.

Table 4. The amounts of reagent (mmol), reflux times of the reactions (hours), crystallisation solvents, yield of the reactions (%), and the melting points of the compounds (^oC).

Compound	Ketone	Paraformaldehyde	Phenethylamine hydrochloride	Time (hours)	Crystallisation solvent	Yield %	Melting Point (°C)
1	8.3	9.9	8.3	7	Ethyl acetate	95	169-171
2	7.4	8.9	7.4	8	Methanol	97	163-165
3	6.6	7.9	6.6	13	Ethanol	94	164-165[a]
4	6.4	7.7	6.4	16	Ethanol	96	195-197[b]
5	7.2	8.6	7.2	12	Ethanol	87	192-194[c]
6	5.0	6.0	5.0	14	Methanol.	97	205-207
7	5.2	6.3	5.2	26	Methanol	91	167-169
8	6.0	7.2	6.0	8	Methanol	98	194-195
9	7.3	8.8	7.3	19	Methanol	93	167-169
10	7.9	9.5	7.9	7	Ethanol	93	156-157

a: Melting point for **3** previously reported [16] as 164-166 °C (from methanol).

b: Melting point for **4** previously reported [28] as 210 °C (from isopropanol).

c: Melting point for **5** previously reported [28] as 200 °C (from acetone).

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Sample Availability: Samples of compounds **1-10** are available from the authors.