Enhanced Nucleophilicity of *N*-Aryl Amides with peri-CH and Their Condensations with Formaldehyde

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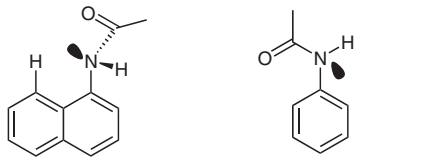
Abstract: *N*-Aryl amides with peri-CH are capable to condense with formaldehyde to yield *N*-hydroxymethylated *N*-aryl amides. The enhanced nucleophilicity is attributed to the single conjugation of the amide nitrogen with the acyl group but not the aryl group. Infrared measurements provide additional evidence for the enhanced nucleophilicity of the amides with peri-CH.

Key words: amides, condensation, nucleophilic addition, aldehydes, alcohols

Amides and their reactions are important in both organic chemistry and biochemistry because many bioactive compounds or their intermediates possess amide groups. One of the reactions of primary and secondary amides is their condensation with formaldehyde to form *N*-hydroxymethyl amides. However, the reaction is limited to primary amides and *N*-alkyl amides.[1] So far, there has been no report on the condensation between *N*-aryl amides and formaldehyde. We believe this is due to the dual conjugation of the lone-pair electrons on the nitrogen atom of the *N*-aryl amides with both the acyl groups and aryl groups.[2] This makes the *N*-aryl amide nitrogen less nucleophilic. If a bulky group located close to the amide group on the aromatic ring can force the acyl group in an out of plane position with respect to the aromatic ring, only single conjugation of the nitrogen lone pair with acyl group is possible (Figure 1). This is supported by many amide structures in the Cambridge Structure Database (CSD).[3] This type of amide with peri-CH would be reactive enough to condense with formaldehyde. To test this idea, we carried out the following experiments.



lone pair inside of the aromatic ring plane for *N*-aryl amide with peri-CH: single conjugation

lone pair outside of the aromatic ring plane for *N*-aryl amide without peri-CH: dual conjugation

Figure 1

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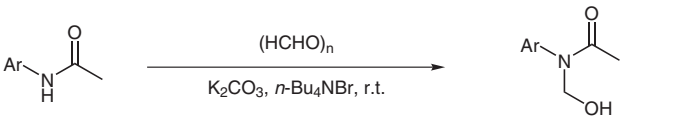
When acetamide **1a** (Table 1) was treated with an equimolar amount of K_2CO_3 and an excess of polyformaldehyde in chloroform at room temperature for 1.5 hours, *N*-hydroxymethyl-*N*-(1-naphthyl)acetamide (**1b**) was formed in 93% yield.

A number of solvents (chloroform, ethyl acetate, toluene, acetone, and THF) and bases (K_2CO_3, Na_2CO_3, $NaHCO_3$, and NaOH) were tested using the hydroxymethylation of acetamide **1a** (Table 1) as the model reaction. It was found that higher yields could be obtained using chloroform as the solvent and K_2CO_3 as the base. Under this conditions, a series of substituted *N*-(1-naphthyl)amides were hydroxymethylated and the results and the structures are given in Table 1. These methanol derivatives of *N*-aryl-substituted secondary amides, which are not stable in solutions, but are stable for two weeks when neat, have not been previous reported in the literature. This type of compounds are useful intermediates in medicinal chemistry and organic synthesis.[4] In control experiments, no hydroxymethylation occurred for **5a**, **9a** (Table 1), and *N*-[1-(8-methylnaphthyl)]acetamide, because the required steric interaction between the peri-CH and the amide group does not exist in these structures. When the steric hindrance of the acyl group increases, both the reaction rate and yield decrease notably. No hydroxymethylated compounds were obtained when the acyl group was pivaloyl (**4a**, Table 1). The differing reaction yield can be explained by the fact that the bulky group hinders the approach of the amide toward the formaldehyde even though the amide is nucleophilic enough. The acyl groups of amides **2a**, **3a**, and **4a** are bulkier than those of amides **1a**, **6a**, **7a, 8a**, and **10a**. Therefore, only the later condensed with formaldehyde efficiently (Table 1).

To expand the scope of the reaction as well as to further demonstrate the existence of the peri-CH with amide-group interaction in other aromatic structures, we examined indole-derived amides, **11a** and **12a**. When **11a** was treated with ten equivalents of polyformaldehyde, **11b** was obtained in 86% yield. On the other hand, when treated with one equivalent of polyformaldehyde, **11a** yielded **11b** and **11c** in ca. 1:1.2 molar ratio in 67% yield. Similar results were obtained when **12a** reacted with ten equivalents and one equivalent of polyformaldehyde (Table 1). We also examined derivatives of *N*-phenylacetamide (**13a**–**22a**, Table 1), but only **13a** and **14a** were hydroxymethylated (Table 1). The hydroxymethylation of

13a and **14a** can be attributed to the larger conformational free energies of the substituents (peri C–CH and C–CH_3),[5] which hinder the conjugation of the nitrogen lone pair with the benzene ring. Therefore the nucleophilicity of amides **13a** and **14a** are strong enough to condense with formaldehyde, although amide **14a** took a longer reaction time.

Table 1 *N*-Hydroxymethylation of *N*-Aryl Amides Using Formaldehyde and K_2CO_3 at Room Temperature[6]



1a–21a **1b–3b**, **6b–8b**, **10b–14b**

15a, Ar = Ph; **16a**, Ar = 2-HOC_6H_4; **17a**, Ar = 2-$MeOC_6H_4$; **18a**, Ar = 3-$O_2NC_6H_4$; **19a**, Ar = 4-$O_2NC_6H_4$; **20a**, Ar = 4-MeC_6H_4; **21a**, Ar = 4-$Me_2CHC_6H_4$; **22a**, Ar = 2,6-$Me_2C_6H_3$

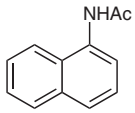
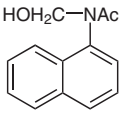
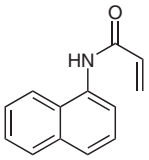
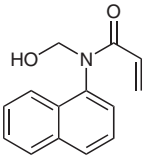
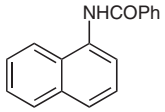
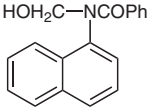
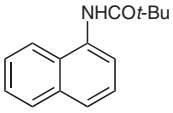
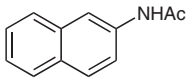
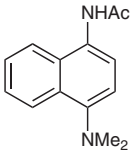
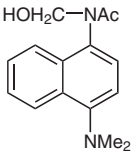
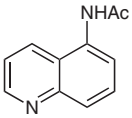
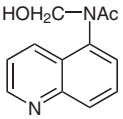
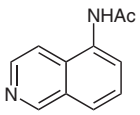
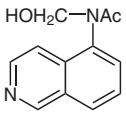
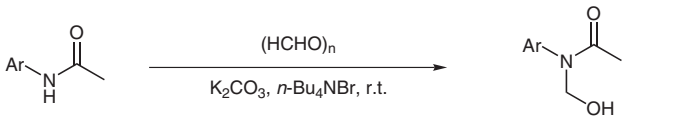
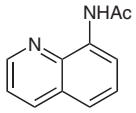
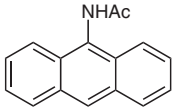
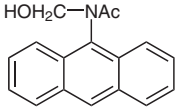
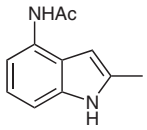
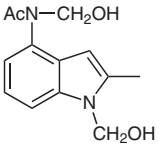
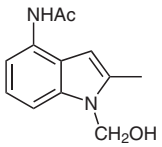
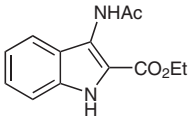
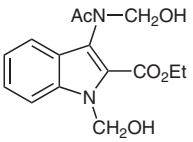
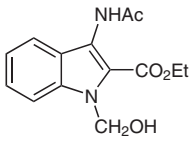
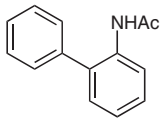
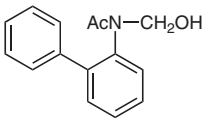
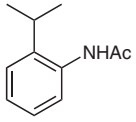
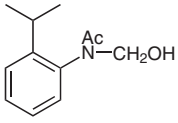
Substrate	Product	Time (h)	Yield (%)[a]
 **1a**	 **1b**	1.5	93
 **2a**	 **2b**	2.5	50[b]
 **3a**	 **3b**	2.5	20
 **4a**	None	24	0
 **5a**	None	24	0
 **6a**	 **6b**	1.5	90
 **7a**	 **7b**	3.0	80
 **8a**	 **8b**	2.0	69

Table 1 *N*-Hydroxymethylation of *N*-Aryl Amides Using Formaldehyde and K_2CO_3 at Room Temperature[6] (continued)



1a–21a **1b–3b**, **6b–8b**, **10b–14b**

15a, Ar = Ph; **16a**, Ar = 2-HOC_6H_4; **17a**, Ar = 2-$MeOC_6H_4$; **18a**, Ar = 3-$O_2NC_6H_4$;
19a, Ar = 4-$O_2NC_6H_4$; **20a**, Ar = 4-MeC_6H_4; **21a**, Ar = 4-$Me_2CHC_6H_4$; **22a**, Ar = 2,6-$Me_2C_6H_3$

Substrate	Product	Time (h)	Yield (%)[a]
 **9a**	None	24	0
 **10a**	 **10b**	4.0	87
 **11a**	 **11b**  **11c**	5.0	86
 **12a**	 **12b**  **12c**	3.0	67[b,c]
 **13a**	 **13b**	5.0	93[b]
 **14a**	 **14b**	15	80

[a] Yield from ^1H NMR.
[b] Isolated yield.
[c] One equivalent polyformaldehyde.

Table 2 Carbonyl IR Data for *N*-Aryl Amides[a]

Amide	$\nu_{C=O}$ (cm^{-1})
1a	1655
2a	1658
3a	1649
4a	1650
5a	1668
6a	1650
7a	1656
8a	1660
9a	1677
10a	1648
11a	1636
12a	1660
13a	1661
14a	1654
15a	1664
16a	1667
17a	1669
18a	1676
19a	1680
20a	1661
21a	1661
22a	1651

[a] Measured on KBr disc.

We reasoned that when the amide group interacts with peri-CH, the lone pair is perpendicular to the π-orbital of the aromatic ring and is not in a favorable position to conjugate with the aromatic ring. Consequently, it is more likely that it would conjugate better with the acyl group. This would lead to lower vibrational frequencies of the hydroxymethylatable amides. Infrared measurements confirmed that this was indeed the case. Most of the carbonyl groups of hydroxymethylatable substrates (**1a**–**3a**, **6a**–**8a**, and **10a**–**14a**) have lower frequencies (<1661 cm^{-1}) than those amides which cannot be hydroxymethylated (**5a**, **9a**, and **15a**–**22a**, Table 2). Amide **4a** has a low frequency (1650 cm^{-1}) but cannot be hydroxymethylated because the sterochemical effect of the tertiary butyl group hinders the approach of formaldehyde to the amide.

In summary, we have developed a simple and efficient procedure for hydroxymethylation of *N*-aryl amides that possess a peri-CH and amide-group interaction. The enhanced nucleophilicity of the *N*-aryl amides is attributed to the single conjugation of the amide nitrogen lone pair with the acyl group. The *N*-aryl groups include phenyl, naphthyl, anthryl, indolyl, and biphenyl. This represents an example of designing a synthetic reaction based on peri-CH and amide group interaction. The experiment results and the infrared data presented herein support the peri-CH interaction of the *N*-aryl amides.

Acknowledgment

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References and Notes

(1) (a) Gupta, R.; Paul, S.; Nanda, P. *J. Indian Chem. Soc.* **2005**, *82*, 573. (b) Winstead, M. B.; Heine, H. W. *J. Am. Chem. Soc.* **1955**, *77*, 1913. (c) Zhong, W.; Song, G.; Peng, Y.; Qian, X. *Synth. Commun.* **2000**, *30*, 3801.

(2) (a) Haisa, M.; Kashino, S.; Ueno, T.; Shinozaki, N.; Matsuzaki, Y. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *36*, 2306. (b) Wasserman, H. J.; Ryan, R. R.; Layne, S. P. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *41*, 783.

(3) (a)Cambridge Structural Database, version 1.8 (May 2007). (a) Molcanov, K.; Stojkovic, M. R.; Piantanida, I.; Zinic, M. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2006**, *62*, o2666. (b) Balasubramamam, V.; Mohamed-Abubakar, S.; Vittal, J. J.; Valiyaveettil, S. *CrystEngComm* **2004**, *6*, 284. (c) Klika, K. D.; Janovec, L.; Lmrich, J.; Suchar, G.; Kristian, P.; Sillanpaa, R.; Pihlaja, K. *Eur. J. Org. Chem.* **2002**, 1248.

(4) (a) Royo, M.; Alsina, J.; Giralt, E.; Slomcyznska, U.; Albericio, F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1095. (b) Pianka, M.; Edwards, J. D.; Smith, C. B. F. *J. Sci. Food Agric.* **1966**, *17*, 407. (c) Haworth, R. D.; MacGillivary, R.; Peacock, D. H. *J. Chem. Soc.* **1950**, 1493.

(5) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

(6) **Typical Experimental Procedure for Hydroxymethylation of *N*-Aryl Amides**
A mixture of amides (0.54 mmol, 1 equiv), polyformaldehyde (5.40 mmol, 10 equiv), K_2CO_3 (0.54 mmol, 1 equiv), and PTC (TBAB, 0.02 mmol, 0.05 equiv) in dry $CHCl_3$ was stirred for the indicated time (Table 1) at r.t. After completion of the reaction, the unreacted polyformaldehyde was removed by filtration and $CHCl_3$ was removed under vacuum to obtain the crude products. The crude products were purified by preparative TLC on SiO_2 or analyzed by ^1H NMR to determine the yields.
Spectroscopic Data for Products (Table 1)
***N*-Hydroxymethyl-*N*-(naphthalen-1-yl)acetamide (1b)**
White syrup, EtOAc–CH_2Cl_2 (1:8) as eluant, 93% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.965–7.891 (m, 3 H), 7.613–7.549 (m, 2 H), 7.505 (t, *J* = 7.5 Hz, 1 H), 7.446 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 5.374 (d, *J* = 10.0 Hz, 1 H), 4.915 (d, *J* = 10.0 Hz, 1 H), 4.320–4.293 (br m, 1 H), 1.803 (s, 3 H). ESI-MS: *m/z* (%) = 216.0 (100) [M^+ + 1]. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.50; H, 6.10; N, 6.55. IR (KBr): 3350.23, 3052.62, 2951.26, 1649.64, 1052.16, 1037.96 cm^{-1}.
***N*-Hydroxymethyl-*N*-(naphthalen-1-yl)acrylamide (2b)**
White syrup, EtOAc–CH_2Cl_2 (1:8) as eluant, 50% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.941–7.905 (m, 3 H), 7.587–7.565 (m, 2 H), 7.518–7.487 (m, 1 H), 7.428–7.412 (m, 1 H), 6.444 (dd, J_1 = 17.0 Hz, J_2 = 2.0 Hz, 1 H), 5.812 (dd,

J_1 = 17.0 Hz, J_2 = 10.0 Hz, 1 H), 5.478 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1 H), 5.441 (dd, J_1 = 10.0 Hz, J_2 = 7.0 Hz, 1 H), 5.002 (dd, J_1 = 10.0 Hz, J_2 = 9.0 Hz, 1 H), 4.329 (t, J = 8.0 Hz, 1 H). ESI-MS: *m/z* = 228.0 (100) [M^+ + 1]. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.97; H, 5.79; N, 6.17. IR (KBr): 3398.72, 3055.21, 2928.00, 1653.31, 1049.45, 1029.40 cm^{-1}.

***N*-Hydroxymethyl-*N*-(naphthalen-1-yl)benzamide (3b)**

White syrup, Et_2O–CH_2Cl_2 (1:15) as eluant, 20% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.156 (d, J = 8.0 Hz, 1 H), 7.890 (d, J = 8.0 Hz, 1 H), 7.748 (d, J = 13.0 Hz, 1 H), 7.655 (t, J = 7.5 Hz, 1 H), 7.585–7.542 (m, 2 H), 7.299–7.246 (m, 3 H), 7.190 (t, J = 7.5 Hz, 1 H), 7.098–7.045 (m, 3 H), 5.541 (t, J = 9.0 Hz, 1 H), 5.096 (t, J = 9.0 Hz, 1 H), 4.207 (t, J = 9.0 Hz, 1 H). ESI-MS: *m/z* (%) = 278.0 [M^+ + 1]. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.97; H, 5.43; N, 5.08. IR (KBr): 3409.95, 3057.77, 2927.19, 1636.20, 1055.98, 1019.09 cm^{-1}.

***N*-[4-(Dimethylamino)naphthalen-1-yl]-*N*-(hydroxymethyl)acetamide (6b)**

Colorless syrup, Et_2O–CH_2Cl_2 (1:6) as eluant, 90% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.302–8.283 (m, 1 H), 7.911–7.892 (m, 1 H), 7.583–7.542 (m, 2 H), 7.327 (d, J = 8.0 Hz, 1 H), 7.037 (d, J = 8.0 Hz, 1 H), 5.353–5.325 (m, 1 H), 4.892–4.861 (m, 1 H), 4.048 (br s, 1 H), 2.932 (s, 6 H), 1.811 (s, 3 H). ESI-MS: *m/z* (%) = 258.9 [M^+]. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.73; H, 7.03; N, 10.83. IR (KBr): 3412.11, 354.34, 2926.98, 1652.68, 1047.83, 970.03 cm^{-1}.

***N*-Hydroxymethyl-*N*-(quinolin-5-yl)acetamide (7b)**

White solid, CH_2Cl_2–Et_2O (1:2) as eluant, 80% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.980 (dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1 H), 8.362 (d, J = 8.5 Hz, 1 H), 8.164 (d, J = 8.5 Hz, 1 H), 7.758–7.726 (m, 2 H), 7.523–7.492 (m, 2 H), 5.187–5.152 (m, 1 H), 5.129–5.094 (m, 1 H), 4.383 (br t, J = 7.0 Hz, 1 H), 1.178 (s, 3 H). ESI-MS: *m/z* (%) = 216.9 (100) [M^+]. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.64; H, 5.60; N, 12.95. IR (KBr): 3266.71, 3192.02, 2926.37, 1660.64, 1051.17, 1000.55 cm^{-1}.

***N*-Hydroxymethyl-*N*-(isoquinolin-5-yl)acetamide (8b)**

White syrup, EtOH–CH_2Cl_2 (1:15) as eluant, 69% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.331 (s, 1 H), 8.631 (d, J = 6.0 Hz, 1 H), 8.049 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 7.797 (d, J = 6.0 Hz, 1 H), 7.695–7.652 (m, 2 H), 5.300 (d, J = 10.5 Hz, 1 H), 4.989 (d, J = 10.5 Hz, 1 H), 1.791 (s, 3 H). ESI-MS: *m/z* (%) = 216.9 (100) [M^+]. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.66; H, 5.60; N, 12.95. IR (KBr): 3247.57, 2922.58, 1667.28, 1054.27, 1032.91 cm^{-1}.

***N*-(Anthracen-9-yl)-*N*-(hydroxymethyl)acetamide (10b)**

Yellow solid, PE–EtOAc (1:1) as eluant, 87% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.537 (s, 1 H), 8.135 (d, J = 8.5 Hz, 2 H), 8.077 (d, J = 8.5 Hz, 2 H), 7.612 (d, J = 7.0 Hz, 2 H), 7.545 (t, J = 7.0 Hz, 2 H), 5.270 (d, J = 8.0 Hz, 2 H), 4.344 (br t, J = 7.5 Hz, 1 H), 1.674 (s, 3 H). ESI-MS: *m/z* (%) = 266.0 (100) [M^+ + 1]. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.97; H, 5.71; N, 5.30. IR (KBr): 3331.89, 3056.89, 2951.33, 1645.44, 1051.71, 1005.03 cm^{-1}.

***N*-Hydroxymethyl-*N*-[1-(hydroxymethyl)-2-methyl-1*H*-indol-4-yl]acetamide (11b)**

Light yellow syrup, PE–EtOAc (1:1) as eluant, 86% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.395 (d, J = 8.0 Hz, 1 H), 7.158 (t, J = 7.5 Hz, 1 H), 6.931 (d, J = 7.5 Hz, 1 H), 6.258 (s, 1 H), 5.623–5.614 (m, 2 H), 5.061–5.037 (m, 2 H), 3.861 (br t, J = 6.5 Hz, 1 H), 3.322 (br t, J = 5.5 Hz, 1 H), 2.509 (s, 3 H), 1.787 (s, 3 H). ESI-MS: *m/z* (%) = 248.9 (100) [M^+]. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.88; H, 6.52; N, 11.27. IR (KBr): 3391.72, 2922.62, 1637.66, 1037.87, 992.20 cm^{-1}.

Ethyl 1-Hydroxymethyl-3-[*N*-(hydroxymethyl)-acetamido]-1*H*-indole-2-carboxylate (12b)

Colorless syrup, Et_2O–CH_2Cl_2 (1:5) as eluant, 65% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.662 (d, J = 8.0 Hz, 1 H), 7.568 (d, J = 8.5 Hz, 1 H), 7.468 (t, J = 7.5 Hz, 1 H), 7.269 (t, J = 7.5 Hz, 1 H), 5.838–5.753 (m, 2 H), 5.313–5.279 (m, 1 H), 4.854 (t, J = 9.5 Hz, 1 H), 4.568 (t, J = 8.5 Hz, 1 H), 4.445–4.385 (m, 2 H), 3.822 (t, J = 7.5 Hz, 1 H), 1.885 (s, 3 H), 1.392 (t, J = 7.0 Hz, 3 H). ESI-MS: *m/z* (%) = 329.0 (100) [M^+ + 23]. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.1. Found: C, 58.80; H, 5.93; N, 9.15. IR (KBr): 3272.07, 2924.23, 1702.18, 1661.32, 1036.68 cm^{-1}.

Ethyl 3-Acetamido-1-(hydroxymethyl)-1*H*-indole-2-carboxylate (12c)

White solid, Et_2O–CH_2Cl_2 (1:5) as eluant, 29% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.538 (s, 1 H), 7.958 (d, J = 7.5 Hz, 1 H), 7.453 (d, J = 8.0 Hz, 1 H), 7.406 (t, J = 6.5 Hz, 1 H), 7.165 (t, J = 6.5 Hz, 1 H), 5.751 (d, J = 8.0 Hz, 2 H), 4.483 (q, J = 7.0 Hz, 2 H), 4.060 (br t, J = 6.0 Hz, 1 H), 2.278 (s, 3 H), 1.487 (t, J = 7.0 Hz, 3 H). ESI-MS: *m/z* (%) = 277.1 (100) [M^+ + 1]. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.85; H, 5.85; N, 10.13. IR (KBr): 3266.87, 2924.45, 1691.19, 1660.78, 1053.51, 1018.17 cm^{-1}.

***N*-(Biphenyl-2-yl)-*N*-(hydroxymethyl)acetamide (13b)**

White solid, EtOAc–PE (1:3) as eluant, 80% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.451–7.361 (m, 8 H), 7.305–7.288 (m, 1 H), 5.299–5.271 (m, 1 H), 4.428–4.389 (m, 1 H), 3.753 (br s, 1 H), 1.780 (s, 3 H). ESI-MS: *m/z* (%) = 263.9 (100) [M^+ + 23]. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.68; H, 6.26; N, 5.83. IR (KBr): 3323.07, 2953.33, 1642.20, 1050.97, 1010.89 cm^{-1}.

***N*-Hydroxymethyl-*N*-(2-isopropylphenyl)acetamide (14b)**

Colorless syrup, Et_2O–CH_2Cl_2 (1:5) as eluant, 50% yield. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.404 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 7.372 (dt, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1 H), 7.231 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.162 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1 H), 5.234 (dd, J_1 = 10.0 Hz, J_2 = 7.0 Hz, 1 H), 4.744 (t, J = 10.0 Hz, 1 H), 4.002 (t, J = 8.0 Hz, 1 H), 3.124 (m, 1 H), 1.818 (s, 3 H), 1.231 (d, J = 6.5 Hz, 3 H), 1.203 (d, J = 7.0 Hz, 3 H). ESI-MS: *m/z* (%) = 208.0 (100) [M^+ + 1]. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.52; H, 8.28; N, 6.75. IR (KBr): 3326.96, 2963.94, 1652.29, 1048.75, 1027.57 cm^{-1}.