Tetrahedron Letters 49 (2008) 4742–4745

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Azido-Schmidt reaction for the formation of amides, imides and lactams from ketones in the presence of $FeCl_3$

J. S. Yadav *, B. V. Subba Reddy, U. V. Subba Reddy, K. Praneeth

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 21 April 2008
Revised 22 May 2008
Accepted 25 May 2008
Available online 13 June 2008

Keywords:
Schmidt reaction
Ketones
Sodium azide
Amides
Imides and lactams

ABSTRACT

Ketones undergo smooth rearrangement with $TMSN_3$ in the presence of $FeCl_3$ under extremely mild conditions to provide the corresponding amides, imides and lactams in good yields with high selectivity. This method is very useful for the preparation of a wide range of amides, imides and lactams from ketones. The use of $FeCl_3$ makes this method simple, convenient and cost-effective.

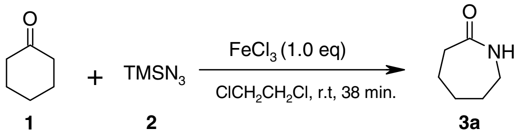
The amide bond is one of the most important linkages in peptide chemistry. Although the majority of amide bonds are formed by condensation of an amine and a carboxylic acid, alternative approaches to amide synthesis are of continuing interest.[1] The Schmidt reaction is a valuable transformation for the synthesis of amides and lactams from aldehydes and ketones.[2] It accomplishes both the cleavage of a carbon–carbon bond and the formation of a carbon–nitrogen bond. It represents a powerful method particularly for manufacturing amides and lactams in the chemical industry.[3] However, the classical Schmidt reaction requires strong protic acids, such as concentrated sulfuric acid and trichloroacetic acid, which result in a large number of byproducts and serious corrosion problems.[4] Furthermore, in situ generated hydrazoic acid is unstable and also explodes at high temperature. Since the classical Schmidt reaction was effected in strongly acidic media, this precludes its application to acid-sensitive substrates. Although the Schmidt reaction utilizes hydrazoic acid as a nitrogen source, it is now known that alkyl azides can be used in Schmidt chemistry.[5–7] Trimethylsilyl azide has been used as a safe and convenient azide source for various organic transformations.[8]

In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions.[9] Moreover, iron salts are inexpensive, easy to handle and are environmentally friendly. However, there have been no reports on the use of the $FeCl_3$/$TMSN_3$ system for the Schmidt reaction.

In this Letter, we disclose a versatile and convenient approach for the preparation of amides, imides and lactams from ketones by means of the azido-Schmidt reaction. Whilst working on the nucleophilic addition reactions of carbonyl compounds with $TMSN_3$ in the presence of $FeCl_3$, surprisingly, we observed the formation of amides. This provided incentive for an extensive study. Initially, we examined the reaction of cyclohexanone with $TMSN_3$ in the presence of a stoichiometric amount of $FeCl_3$. The reaction proceeded rapidly in dichloroethane at 23 °C and the product, caprolactam **3a** was isolated in 82% yield (Scheme 1).

Encouraged by this result, we turned our attention to various cyclic ketones such as cycloheptanone, 1,4-cyclohexanedione, cyclododecanone, 1-tetralone, 2-phenylchroman-4-one and 2-tetralone. These cyclic ketones were converted successfully into their corresponding lactams by using this procedure (Table 1, entries **b**–**g**).

Next, we examined the reactivity of α-ketoamides and a 1,2,3-triketone. Interestingly, isatin and 5-methylisatin underwent facile ring expansion under these conditions (Table 1, entries **h** and **i**). Ninhydrin also participated in this reaction (Table 1, entry **j**). Interestingly, acyclic ketones such as acetophenone, propiophenone, 4-hydroxyacetophenone, 4-iodoacetophenone and benzophenone



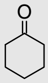
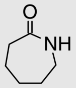
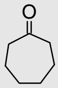
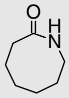
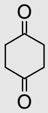
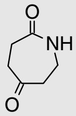
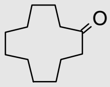
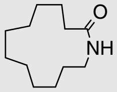
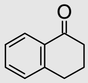
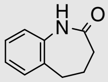
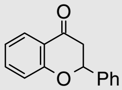
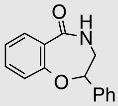
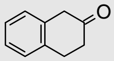
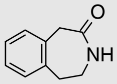
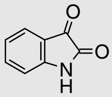
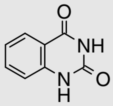
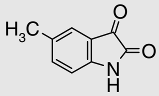
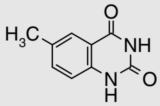
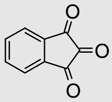
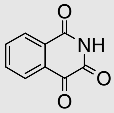
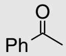
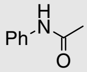
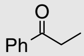
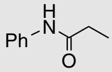
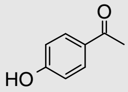
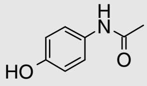
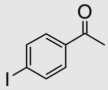
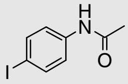
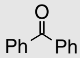
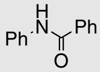
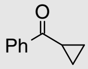
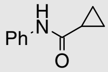
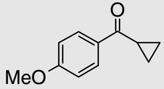
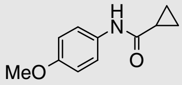
Scheme 1.

---

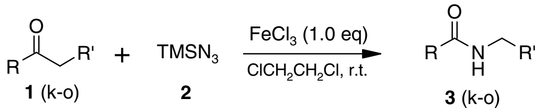
* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J. S. Yadav).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.113

Table 1
$FeCl_3$-mediated Schmidt reaction of various ketones with $TMSN_3$/NaN_3

Entry	Substrate	Product[a]	$FeCl_3/TMSN_3$		$FeCl_3/NaN_3$	
			Time (min)	Yield[b] (%)	Time (h)	Yield[b] (%)
a			38	82	3.0	70
b			45	80	3.0	72
c			55	68	3.5	68
d			65	81	4.0	65
e			40	80	2.5	75
f			50	75	3.0	68
g			46	70	2.5	67
h			30	80	2.5	74
i			35	75	2.5	75
j			40	82	3.0	72
k			30	85	2.0	76
l			35	78	2.0	70
m			33	72	2.5	66
n			35	76	3.0	68
o			32	79	2.5	70
p			45	81	3.5	73
q			49	78	3.5	70

[a] All products were characterized by NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.

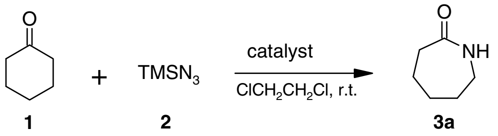


Scheme 2.

underwent a smooth rearrangement to furnish the corresponding secondary amides in good yields (Scheme 2, Table 1, entries **k**–**o**).

Similarly, aryl cyclopropyl ketones such as phenyl cyclopropyl ketone and *p*-methoxyphenyl cyclopropyl ketone also gave the respective anilides (Table 1, entries **p** and **q**). The products were characterized by ^{1}H and ^{13}C NMR, IR and mass spectrometry. As solvent, 1,2-dichloroethane gave the best results. It is noteworthy to mention that the reaction also proceeded smoothly with sodium azide instead of TMSN$_3$ albeit with longer reaction times and the results are presented in Table 1. The azido-Schmidt reaction involves the addition of azide to the ketone followed by rearrangement and ring expansion. Similar to the classical Schmidt reaction, the mechanism would involve simple Lewis acid activation of the carbonyl group followed by the addition of azide. The resulting iminodiazonium ions, which by loss of nitrogen and migration of the *anti*-substituent, either an alkyl or aryl group, to the electron-deficient nitrogen gives the amide (Scheme 3).[10,11]

Table 2
The effects of various Lewis acid catalysts on the preparation of **3a**



Entry	Catalyst (equiv)	Time (h)	Yield[a] (%)
1	FeCl$_3$ (1.0)	0.5	82
2	FeCl$_3$ (0.1)	12	78
3	InBr$_3$ (0.5)	3	40
4	InCl$_3$ (0.5)	3	30
5	ZrCl$_4$ (0.5)	5	15
6	YbCl$_3$ (0.5)	12	No reaction
7	Bi(OTf)$_3$ (0.5)	12	No reaction
8	In(OTf)$_3$ (0.5)	12	No reaction
9	Sm(OTf)$_3$ (0.5)	12	No reaction
10	Yb(OTf)$_3$ (0.5)	12	No reaction
11	Sc(OTf)$_3$ (0.5)	12	No reaction
12	CuI (1.0)	12	No reaction
13	YCl$_3$ (0.5)	12	No reaction
14	I$_2$ (2.0)	12	No reaction
15	IBX (0.5)	14	No reaction
16	CAN (2.0)	14	No reaction
17	Oxone (1.5)	14	No reaction

[a] Yield refers to pure products after chromatography.

For alkyl aryl ketones, aryl migration appears to be predominant unless the alkyl group is bulky.[11] For example, simple alkyl aryl ketones gave the corresponding amides by preferential migration of the aryl group over the alkyl group. Similarly, cyclopropyl aryl ketones afforded the amide with preferential migration of the aryl group over the cyclopropyl moiety.[12] In the case of benzocycloalkenylketones with an ether linkage *ortho* or *para* to the carbonyl group, the alkyl migration was concurrent with aryl migration.[13] For example, flavanone (chroman-4-one), on treatment with TMSN$_3$/FeCl$_3$, underwent exclusive alkyl migration to afford the 2-phenyl-1,4-benzoxazepin-5-(4*H*)-one (Table 1, entry **f**, Scheme 3).[13] Although phenyl migration was observed in the case of 1-tetralone, conversely, alkyl migration was observed with 2-tetralone which was consistent with previous reports.[14] With α-diketones, exclusive carbonyl migration was observed during the azido-Schmidt reaction, which was similar to the Baeyer–Villiger reaction.[15] In all cases, the rearrangement products were identified with authentic samples prepared by reported procedures.[16] In the absence of catalyst, the reaction did not proceed even after a long reaction time (10–24 h). Furthermore, we have examined the possibility of FeCl$_3$ functioning catalytically or, at least, in less than stoichiometric amounts. Interestingly, the reaction was also successful with 10 mol % FeCl$_3$, albeit a long reaction time was required (12 h, Table 2). The effects of various Lewis acids such as InCl$_3$, InBr$_3$, ZrCl$_4$, YbCl$_3$ and YCl$_3$ were studied for this conversion, and the results are presented in Table 2. Of these catalysts, anhydrous FeCl$_3$ was found to be the most effective in terms of conversion. Various metal triflates such as Bi(OTf)$_3$, In(OTf)$_3$, Sm(OTf)$_3$, Yb(OTf)$_3$ and Sc(OTf)$_3$ were found to be ineffective for this conversion. The scope and generality of this process is illustrated with respect to various ketones, and the results are presented in Table 1.[17] The advantages of this procedure include mild reaction conditions as well as short reaction times, easy work-up and good yields.

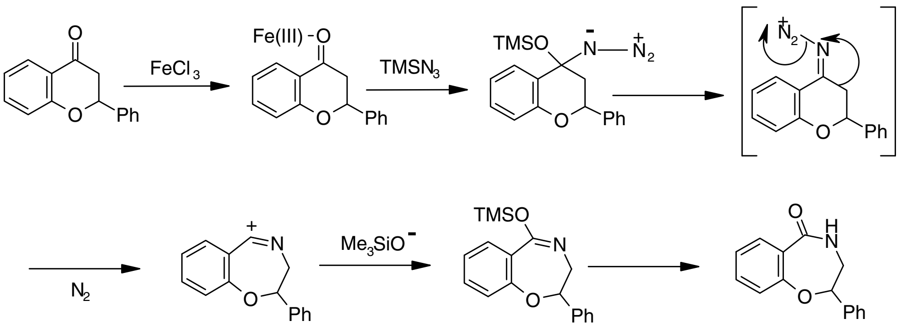
In summary, anhydrous FeCl$_3$ has proved to be a useful and highly efficient reagent for the azido-Schmidt reaction of ketones with TMSN$_3$ under mild conditions. In addition to its simplicity and efficiency, this method produces amides, imides and lactams in good to excellent yields in short reaction times. This method provides an access to a wide range of potentially valuable lactams.

Acknowledgement

U.V.S.R. and K.P. thank UGC New Delhi for the award of fellowships.

References and notes

1. For recent reviews on chemical methods for amide synthesis, see: (a) Albericio, F. *Curr. Opin. Chem. Biol.* **2004**, *8*, 211–221; (b) Mahajan, Y. R.; Weinreb, S. M. *Sci. Synth.* **2005**, *21*, 17–25; (c) Ziegler, T. *Sci. Synth.* **2005**, *21*, 43–75; (d) Bode, J. W. *Curr. Opin. Drug Discov. Dev.* **2006**, *9*, 765–775.
2. (a) Schmidt, K. F. *Angew. Chem.* **1923**, *36*, 511–524; (b) Schmidt, K. F. *Chem. Ber.* **1924**, *57*, 704–706.



Scheme 3.

3. Krow, G. R. *Tetrahedron* **1981**, *37*, 1283–1307.
4. (a) McEwen, W. E.; Conrad, W. E.; Vanderwerf, C. A. *J. Am. Chem. Soc.* **1952**, *74*, 1168–1171; (b) Smith, P. A. S.; Horwitz, J. P. *J. Am. Chem. Soc.* **1950**, *72*, 3718–3722.
5. For reviews, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240; (b) Lang, S.; Murphy, J. A. *Chem. Soc. Rev.* **2006**, *35*, 146–156; (c) Nyfeler, E.; Renaud, P. *Chimia* **2006**, *60*, 276–284.
6. (a) Briggs, L. H.; De Ath, G. C.; Ellis, S. R. *J. Chem. Soc.* **1942**, 61–63; (b) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320–323; (c) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291–5294; (d) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.-k.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183–10194; (e) Pearson, W. H.; Fang, W.-k.; Kampf, J. W. *J. Org. Chem.* **1994**, *59*, 2682–2684; (f) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **1995**, *60*, 4960–4961; (g) Pearson, W. H. *J. Heterocycl. Chem.* **1996**, *33*, 1489–1496; (h) Pearson, W. H.; Fang, W.-k. *Isr. J. Chem.* **1997**, *37*, 39–46.
7. (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966; (b) Aube, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637; (c) Aube, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141–1147; (d) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459; (e) Mossman, C. J.; Aube, J. *Tetrahedron* **1996**, *52*, 3403–3408; (f) Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232; (g) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aube, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922.
8. (a) Groutas, W. C.; Felker, D. *Synthesis* **1980**, 861–868; (b) Colvin, E. W. Silicon Reagents for Organic Synthesis, San Diego, **1983**.
9. (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254; (b) Ruping, M.; Nactshim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717–3719; (c) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938–2941; (d) Kischel, J.; Jovel, I.; Mertins, K.; Zapf, A.; Beller, M. *Org. Lett.* **2006**, *8*, 19–22; (e) Diaz, D. D.; Miranda, P. O.; Padron, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457–476; (f) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.
10. Smith, P. A. S. In *Molecular Rearrangements. Part I*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; p 510.
11. Kate, P. T.; Mphalele, M. J.; Brown, M. E. *J. Chem. Soc., Perkin Trans. 2* **1995**, 835–838.
12. Bunce, S. C.; Cloke, J. B. *J. Am. Chem. Soc.* **1953**, *76*, 2244–2248.
13. Misiti, D.; Rimatori, V. *Tetrahedron Lett.* **1970**, *11*, 947–950.
14. (a) Knunyants, L.; Fabrichnyi, B. P. *Dok. Akad. Nauk. S.S.S.R.* **1949**, *68*, 523–526; Knunyants, L.; Fabrichnyi, B. P. *Chem. Abstr.* **1950**, 1469; (b) Katoh, M.; Inoue, H.; Honda, T. *Heterocycles* **2007**, *72*, 497–516.
15. ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4123.
16. (a) Eshghi, H.; Hassankhani, A. *J. Korean Chem. Soc.* **2007**, *51*, 361–364; (b) Arisawa, M.; Yamaguchi, M. *Org. Lett.* **2001**, *3*, 311–312; (c) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272–6274; (d) Ramalingan, C.; Park, Y. T. *J. Org. Chem.* **2007**, *72*, 4536–4538; (e) Eshghi, H.; Gordi, Z. *Synth. Commun.* **2003**, *33*, 2971–2978; (f) Capuano, G.; Giammanco, L. *Gazz. Chim. Ital.* **1956**, *86*, 119; (g) Ling, K. Q.; Ye, J. H.; Chen, X. Y.; Ma, D. J.; Xu, J. H. *Tetrahedron* **1999**, *55*, 9185–9204.

17. *General procedure*: To a stirred solution of ketone (1.0 mmol) in 1,2-dichloroethane (5 mL) were added TMSN$_3$(1.5 mmol) and FeCl$_3$ (1.0 mmol). The resulting mixture was stirred at room temperature for the appropriate time (Table 1). After complete conversion as indicated by TLC, the solvent was removed by evaporation and the residue was diluted with water and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh) using ethyl acetate/hexane (4:6) as eluent to afford the pure derivative. Replacing TMSN$_3$ with NaN$_3$, the same procedure afforded the same products in relatively longer reaction times (Table 1).

Compound **3d**: *1-azacyclotridecan-2-one (Table 1, entry* **d***): White solid, mp = 143–145 °C. IR (KBr)* ν_{max}: 3307, 3082, 2931, 2856, 1639, 1550, 1448, 1283, 1185, 739, 691 cm^{-1}. ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz): δ 7.23 (br s, 1H), 3.21–3.12 (m, 2H), 2.14–2.09 (m, 2H), 1.64–1.19 (m, 18H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 173.5, 38.9, 36.7, 28.1, 26.6, 26.2, 26.1, 25.6, 25.1, 24.8, 24.5, 23.8; LCMS: *m/z*: 198 (M+H)$^+$. HRMS calcd for C$_{12}$H$_{24}$NO (M+H)$^+$: 198.1857. Found: 198.1855.

Compound **3f**: *3,4-Dihydro-2-phenylbenzo[f][1,4]oxazepin-5(2H)-one* (Table 1, entry **f**): Light brown solid, mp = 126–127 °C. IR (KBr) ν_{max}: 3405, 3035, 2924, 2853, 1743, 1608, 1484, 1230, 1113, 1032, 769, 696 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 8.60–8.57, (m, 1H), 7.53–7.42 (m, 6H), 7.29–7.23 (m, 2H), 7.17–7.14 (m, 1H), 5.22 (dd, *J* = 1.5, 8.3 Hz, 1H), 5.11 (dd, *J* = 1.5, 13.2 Hz, 1H), 4.82 (dd, *J* = 9.8, 4.7 Hz, 1H); ^{13}C NMR (CDCl$_3$ + DMSO, 100 MHz): δ 158.6, 151.8, 136.4, 132.1, 129.0, 128.0, 127.9, 125.1, 122.8, 120.5, 112.0, 77.7, 54.9; LCMS: *m/z*: 239 (20, M)$^+$, 218 (30), 192 (100), 139 (50), 116 (75).

Compound **3g**: *2,3,4,5-tetrahydro-1H-3-benzazepin-2-one* (Table 1, entry **g**): pale yellow solid, mp = 148–150 °C. IR (KBr) ν_{max}: 3420, 2924, 2855, 1732, 1523, 1457, 1246, 1081, 754 cm^{-1}. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.40–7.28 (m, 4H), 5.62 (s, 2H), 4.62 (br s, 1H), 3.41–3.33 (m, 2H), 3.26–3.21 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 172.6, 135.4, 131.2, 130.1, 128.8, 127.1, 124.6, 42.1, 40.0, 34.3; LCMS: *m/z*: 184 (100) (M+Na)$^+$.

Compound **3h**: *Quinazoline-2,4-(1H,3H)-dione* (Table 1, entry **h**): White solid, mp = 295–298 °C. IR (KBr) ν_{max}: 3392, 3310, 3106, 3031, 2952, 1695, 1601, 1485, 1355, 1263, 1126, 1009, 756, 649 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz): δ 9.68 (br s, 1H), 9.25 (br s, 1H), 8.13 (d, *J* = 9.5 Hz, 1H), 7.43–7.29 (m, 3H); ^{13}C NMR (CDCl$_3$ + DMSO, 50 MHz): δ 178.3, 154.8, 141.6, 133.3, 132.5, 124.8, 122.6, 121.4; LCMS: *m/z*: 162 (90, M)$^+$, 135 (30), 118 (35), 87 (100).

Compound **3i**: *6-Methylquinazoline-2,4-(1H,3H)-dione* (Table 1, entry **i**): Pale yellow solid mp = 287–289 °C. IR (KBr) ν_{max}: 3457, 3301, 2924, 1682, 1591, 1536, 1302, 1244, 1157, 971, 831, 737, 616 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz) δ: 9.74 (br s, 1H), 7.61 (br s, 1H), 7.42–7.32 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (CDCl$_3$ + DMSO, 50 MHz) δ: 179.2, 154.5, 147.5, 136.4, 134.0, 132.5, 123.6, 116.0, 19.9; LCMS: *m/z*: 199 (70, M+Na)$^+$, 173 (100), 143 (35), 101 (45).

Compound **3j**: *Isoquinoline-1,3,4-(2H)-trione* (Table 1, entry **j**): Light brown solid, mp = 227–229 °C. IR (KBr) ν_{max}: 3448, 2921, 2851, 1750, 1637, 1463, 1379, 1304, 1137, 1051, 712, 647 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz) δ: 10.98 (br s, 1H, NH), 7.78–8.00 (m, 4H); ^{13}C NMR (CDCl$_3$ + DMSO, 100 MHz) δ: 169.8, 159.1, 149.6, 135.4, 134.9, 133.5, 132.6, 132.3, 122.7; EIMS: *m/z*: 174 (20, M − H)$^+$, 147 (M−CO), 132 (20), 104 (100).

Compound **3n**: *N-(4-Iodophenyl)acetamide* (Table 1, entry **n**): Brown solid, mp = 142–144 °C. IR (KBr) ν_{max}: 3304, 3183, 2923, 2852, 1668, 1599, 1483, 1387, 1310, 1250, 1001, 817,726 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz) δ: 9.62 (br s, 1H), 7.54–7.33 (m, 4H), 2.07 (s, 3H); ^{13}C NMR (CDCl$_3$ + DMSO, 100 MHz) δ: 167.8, 137.9, 136.2, 120.5, 85.2, 23.3; LCMS: *m/z*: 283 (M+Na)$^+$; HRMS (ESI): calcd for C$_8$H$_8$NONaI, 283.9548; found, 283.9540.

Compound **3q**: *N-(4-Methoxyphenyl)cyclopropanecarboxamide* (Table 1, entry **q**): White solid, mp = 125–127 °C. IR (KBr) ν_{max}: 3302, 3007, 2922, 2852, 1648, 1532, 1413, 1246, 1175, 1031, 827 cm^{-1}; ^{1}H NMR (CDCl$_3$ + DMSO, 200 MHz) δ: 9.56 (br s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 1.75–1.63 (m, 1H), 0.96–0.86 (m, 2H), 0.76–0.67 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.9, 156.3, 131.1, 121.4, 114.2, 55.5, 15.4, 7.8; LCMS: *m/z*: 192 (M+H)$^+$; HRMS (ESI): calcd for C$_{11}$H$_{14}$NO$_2$, 192.1024; found, 192.1014.