ISSN: 0974 - 7516 Volume 11 Issue 6

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 11(6), 2015 [215-219]

Dimethyl cyanamide as a promoter for the one-pot, three-component synthesis of a novel series of 1,3-oxazines using tetrachlorosilane/zinc chloride as a heterogeneous catalyst

Tamer K.Khatab[1]*, Ebrahim Abdel-Galil[2], Ezzat M.Kandeel[2]

[1]Organometallic and Organometalloid Chemistry Department, National Research Centre, Dokki, Cairo 12622, (EGYPT)

[2]Chemistry Department, Faculty of Science, Mansoura University, Mansoura, (EGYPT)

E-mail: tamer_khatab@hotmail.com

ABSTRACT

The 1,4-dipoles generated from two moles of aromatic ketones have been shown to react efficiently with dimethyl cyanamide via a one-pot [4þ+2] annulation at ambient temperature resulting in the diversity oriented synthesis of a novel series of 1,3-oxazine derivatives through MCR protocol in the presence of tetrachlorosilane - zinc chloride as a heterogeneous promoter.

KEYWORDS

1,4-dipoles, dimethyl cyanamide; 1,3-Oxazine, Tetrachlorosilane; One-pot synthesis.

INTRODUCTION

Multicomponent reactions (MCRs) involving domino processes with at least three different substrates, have emerged as powerful strategies in organic synthesis. These reactions allow molecular complexity and diversity to be created by the facile formation of several new covalent bonds in one-pot transformations. MCRs have found widespread applications in organic, combinatorial and medicinal chemistry[1], and correlate two of the major principles of organic synthesis: convergence and atom economy.

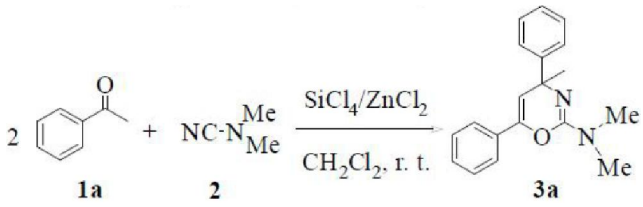
Oxazines have been shown to possess versatile bioactivities, such as antibiotic[2], positive allosteric modulation[3], antispasmodic and analgesic[4]. Even though several methods for the synthesis of 1,3-oxazine derivatives have previously been reported, only a few have been established[5]. Consequently, the development of simple methodologies for the synthesis of 1,3-oxazines is still a challenge in the field of multicomponent reactions. Also, the development of novel MCRs is a challenging task since one has to consider not only the reactivity match of the starting materials, but also the reactivity of the intermediate molecules generated *in situ*, their compatibility and their compartmentalization[6].

Tetrachlorosilane (TCS) has gained increasing importance in the last few years, due to its many positive features. Many research groups have used it to promote reactions such as the formation of amides, hydrazides, dipeptides, carboxyamides and heterocycles and as transsilylating and defluorinating regents. Also, TCS is a weak Lewis acid that has been successfully employed to develop several transformations[7].

Full Paper

RESULTS AND DISSCUSION

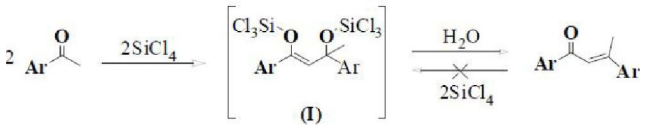
TCS has played a significant role in our research[8] and in continuation of our investigations to develop new methods for the synthesis of heterocyclic compounds and on the design of a novel multicomponent reaction using a binary catalyst derived from TCS as an *in situ* reagent, we have developed an efficient protocol for the synthesis of new series of 1,3-oxazines. The reaction occurs *via* a three-component, one-pot reaction between two moles of acetophenone (1a) and dimethyl cyanamide (2) in the presence of TCS/$ZnCl_2$ in methylene chloride at ambient temperature Scheme 1.



Scheme 1 : Synthesis of *N, N*,4-trimethyl-4,6-diphenyl-4*H*-1,3-oxazine-2-amine (3a)

To optimize the conditions for this reaction, we studied the efficacy of the catalysts molar ratio, the solvent type and the addition sequence. The results obtained are summarized as follows:

It was found that the best results were obtained by using two moles of acetophenone, one mole of dimethyl cyanamide and TCS/$ZnCl_2$ (2:1 by molar ratio), in CH_2Cl_2 TABLE 1, entry 4. Consequently, the optimized reaction conditions are as follows: Ketone (10 mmol), TCS (10 mmol), stirring for 1 h in methylene chloride (20 ml) at ambient temperature, then dimethyl cyanamide (5 mmol) and $ZnCl_2$ (5 mmol) was added. This sequence of addition seemed to be very significant for the formation of very reactive intermediate I, which is thought to be the reaction key step in this reaction. (Scheme 2)



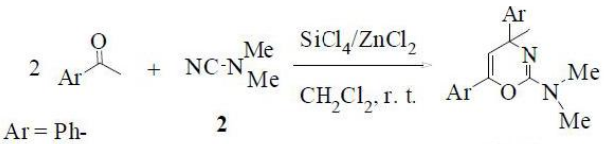
Scheme 2 : The reaction key step

In order to prove that the occurrence of intermediate I as the key step, we stop the reaction after 1 h by work up on water and separate the product which identified as the dypnone by authentic sample and melting point = 172 C as known. This product was reacted with dimethyl cyanamide/$ZnCl_2$ in methylene chloride. The reaction took a very long time 24 h and gave H"10 % yield. This illustrates that the reaction should be run in one pot reaction as explained before, which the intermediate I was formed and then reacts with dimethyl cyanamide in order to obtain good yield and shortest time. These results prompted us to explore the potential of this protocol for the synthesis of various 1,3-oxazines. The results are summarized in Scheme 3 and TABLE 2.

The structures of the obtained 1,3-oxazines were elucidated by spectroscopic methods. The IR spectra showed peaks at 1656 - 1649 and 1636 - 1630 cm^{-1} corresponding to the C=N and C=C (in oxazine ring) groups, respectively. The ^1H NMR spectra of the synthesized products revealed singlets for CH_3 at δ = 1.79 - 1.84, singlets for $–N(CH_3)_2$ at δ = 3.02 and singlets for olefinic protons at δ = 5.76 - 5.83.

TABLE 1 : Effect of the catalysts ratio and the solvent on the yield and reaction time

Entry	Catalysts (molar ratio)	Solvent	Time (h)	Yield (%)[a]
1	No catalyst	CH_2Cl_2	10	0
2	TCS/$ZnCl_2$ (1:1)	CH_2Cl_2	10	30
3	TCS/$ZnCl_2$ (1:2)	CH_2Cl_2	10	32
4	TCS/$ZnCl_2$ (2:1)	CH_2Cl_2	7	75
5	TCS/$ZnCl_2$ (3:1)	CH_2Cl_2	12	78
6	TCS/$ZnCl_2$ (2:1)	THF	10	20
7	TCS/$ZnCl_2$ (2:1)	1,4-dioxane	10	16
8	TCS/$SnCl_2$ (2:1)	CH_2Cl_2	10	65
9	TCS (3)	CH_2Cl_2	10	25
10	$ZnCl_2$ (3)	CH_2Cl_2	10	trace



1a, Ar = Ph-
1b, Ar = 4-Me-C_6H_4-
1c, Ar = 2-Me-C_6H_4-
1d, Ar = 4-MeO-C_6H_4-
1e, Ar = 2-MeO-C_6H_4-
1f, Ar = 4-Cl-C_6H_4-
1g, Ar = 4-Br-C_6H_4-
1h, Ar = 2-thienyl
1i, Ar =2-naphthyl

Scheme 3 : Synthesis of a novel series of 1,3-oxazines

The ^{13}C NMR spectrum of compound 3a showed four characteristic signals at δ = 155.72, 150.34, 133.00 and 132.30 for four quaternary carbons, 130.23-125.11 for $C_{Ar}H$, 100.45 for the olefinic carbon, 56.20 (saturated carbon in oxazine ring), 37.80 ($2CH_3$) and 33.11 (CH_3) ppm.

A plausible theoretical mechanism could be explained and demonstrated as follows: the reaction started by the addition of heterogeneous catalyst $SiCl_4/ZnCl_2$ in a 2:1 molar ratio to the carbonyl group of the aromatic ketones as well as to cyano group in dimethyl cyanamide led to the formation of intermediates (I), (II), respectively, followed by [4+2] cycloaddition to afford 1,3-oxazines.

EXPERMINTAL

All melting points are uncorrected. Microanalyses were carried out by the Microanalytical Laboratory, Cairo University, Cairo, Egypt. Infrared spectra (KBr-disc) were recorded using a Jasco FT/IR-300E spectrometer. ^1H NMR, ^{13}C NMR spectra were measured in $CDCl_3$ using Varian Mercury 300 MHz with chemical shifts using TMS as standard solvent. Mass spectra were recorded on a GC/MS Finnigan SSQ 7000 spectrometer. All reactions were carried out under atmospheric conditions at room temperature. Tetrachlorosilane (TCS), anhydrous zinc chloride were obtained from (Sigma-Aldrich) company. The solvents were distilled and dried over anhydrous calcium chloride before use. Reactions were monitored by TLC on 0.25 mm Merck Silica gel sheets (60 GF 354) (4 × 2 cm), and the spots were detected with UV light.

General procedure for the synthesis of 1,3-oxazines (3a-3i)

In a dry two-necked round-bottomed flask equipped with a rubber septum, a magnetic stir bar and a condenser, a mixture of ketone (10 mmol), tetrachlorosilane (10 mmol) in CH_2Cl_2 (20 ml) was allowed to stir with exclusion of moisture at ambient temperature for 60 min. Dimethyl cyanamide (5 mmol) and anhydrous $ZnCl_2$ (5 mmol) was added and the mixture was stirred for the specified time (TABLE 2). The mixture was poured onto ice–cold H_2O (~100 ml), neutralized with aq. Na_2CO_3 and extracted with $CHCl_3$ (3 x 30 ml). Combined extract dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the obtained residue was purified by crystallization from an appropriate solvent to give product 3.

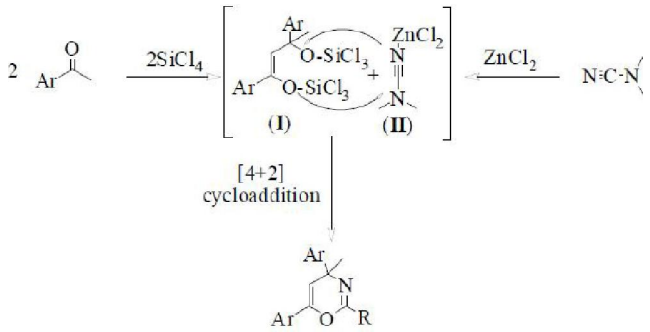
Data for *N*, *N*,4-trimethyl-4,6-diphenyl-4*H*-1,3-oxazine-2-amine (3a) Mp = 85 ºC. IR (KBr): *ν* = 3080, 2920, 2852, 1653, 1632. ^1H NMR (300 MHz,

TABLE 2 : Reaction of various aromatic ketones 1 with dimethyl cyanamide 2

Entry	Ketones	Products	Time (h)	Yield (%)[a]
1	Acetophenone	3a	7	75
2	4-Methylacetophenone	3b	5	77
3	2-Methylacetophenone	3c	8	73
4	4-Methoxyacetophenone	3d	5	78
5	2-Methoxyacetophenone	3e	9	70
6	4-Chloroacetophenone	3f	8	68
7	4-Bromoacetophenone	3g	9	65
8	2-acetylthiphene	3h	7	72
9	2-acetylnaphthalene	3i	10	63

[a]**Isolated yield**

Full Paper



Scheme 4 : Suggested reaction mechanism

$CDCl_3$): δ_H = 1.80 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 5.78 (s, 1H, olefinic), 7.27-7.40 (m, 8H, ArH), 7.77 (d, 2H, *J* = 9, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ_C = 155.72, 150.34, 133.00, 132.30 (4 quaternary carbons), 130.23, 128.80, 127.90, 126.62, 125.93, 125.11 (10 aromatic carbon), 100.45 (olefinic carbon), 56.2 (saturated carbon in oxazine ring), 37.80 ($2CH_3$), 33.11 (CH_3). MS (EI 70 *eV*) *m/z*: 292 (M^+), 277, 248, 220, 105. Anal. Calcd. for $C_{19}H_{20}N_2O$ (292.37): C, 78.05; H, 6.89; N, 9.58. Found: C, 78.00; H, 6.84; N, 9.52.

Data for *N, N*,4-trimethyl-4,6-diptolyl-4*H*-1,3-oxazine-2-amine (3b) Mp = 109 ºC. IR (KBr): *v* = 3082, 2942, 2852, 1649, 1631. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.79 (s, 3H, CH_3), 2.34 (s, 6H, $2CH_3$), 3.01 (s, 6H, $2CH_3$), 5.76 (s, 1H, olefinic), 7.20-7.28 (m, 6H, ArH), 7.32 (d, 2H, *J* = 9, ArH). MS (EI 70 *eV*) *m/z*: 320 (M^+). Anal. Calcd. for $C_{21}H_{24}N_2O$ (320.43): C, 78.71; H, 7.55; N, 8.74. Found: C, 78.67; H, 7.51; N, 8.68.

Data for *N, N*,4-trimethyl-4,6-diotolyl-4*H*-1,3-oxazine-2-amine (3c) Mp = 100 ºC. IR (KBr): *v* = 3082, 2940, 2850, 1650, 1631. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.80 (s, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 3.01 (s, 6H, $2CH_3$), 5.78 (s, 1H, olefinic), 7.20-7.31 (m, 8H, ArH). MS (EI 70 *eV*) *m/z*: 320 (M^+). Anal. Calcd. for $C_{21}H_{24}N_2O$ (320.43): C, 78.71; H, 7.55; N, 8.74. Found: C, 78.66; H, 7.48; N, 8.66.

Data for 4,6-Bis (4-methoxyphenyl)-*N, N*,4-trimethyl-4*H*-1,3-oxazine-2-amine (3d) Mp = 80 ºC. IR (KBr): *v* = 3090, 2943, 2860, 1651, 1633. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.82 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 3.88 (s, 6H, $2CH_3$), 5.79 (s, 1H, olefinic), 7.12-7.21 (m, 6H, ArH), 7.85 (d, 2H, *J* = 8.5, ArH). MS (EI 70 *eV*) *m/z*: 352 (M^+). Anal. Calcd. for $C_{21}H_{24}N_2O$ (352.43): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.52; H, 6.81; N, 7.90.

Data for 4,6-Bis (2-methoxyphenyl)-*N, N*,4-trimethyl-4*H*-1,3-oxazine-2-amine (3e) Mp = 73 ºC. IR (KBr): *v* = 3089, 2943, 2858, 1652, 1633. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.83 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 3.89 (s, 6H, $2CH_3$), 5.81 (s, 1H, olefinic), 7.12-7.75 (m, 8H, ArH). MS (EI 70 *eV*) *m/z*: 352 (M^+). Anal. Calcd. for $C_{21}H_{24}N_2O$ (352.43): C, 71.57; H, 6.86; N, 7.95. Found: C, 71.51; H, 6.83; N, 7.88.

Data for 4,6-Bis (4-chlorophenyl)-*N, N*,4-trimethyl-4*H*-1,3-oxazine-2-amine (3f) Mp = 123 ºC. IR (KBr): *v* = 3090, 2948, 2865, 1655, 1634. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.83 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 5.81 (s, 1H, olefinic), 7.31 (d, 2H, *J* = 9, ArH), 7.42 (d, 2H, *J* = 9, ArH), 7.50-7.56 (m, 4H, ArH). MS (EI 70 *eV*) *m/z*: 361 (M^+), 317, 289, 139. Anal. Calcd. for $C_{19}H_{18}Cl_2N_2O$ (361.27): C, 63.17; H, 5.02; Cl, 19.63; N, 7.75. Found: C, 63.12; H, 4.95; Cl, 19.55; N, 7.70.

Data for 4,6-Bis (4-bromophenyl)-*N, N*,4-trimethyl-4*H*-1,3-oxazine-2-amine (3g) Mp = 135 ºC. IR (KBr): *v* = 3090, 2950, 28656, 1656, 1636. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.83 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 5.83 (s, 1H, olefinic), 7.22 (d, 2H, *J* = 9, ArH), 7.33 (d, 2H, *J* = 9, ArH), 7.66-8.00 (m, 4H, ArH). MS (EI 70 *eV*) *m/z*: 450 (M^+). Anal. Calcd. for $C_{19}H_{18}Br_2N_2O$ (450.17): C, 50.69; H, 4.03; Br, 35.50; N, 6.22. Found: C, 50.62; H, 3.96; Br, 35.45; N, 6.18.

Data for *N, N*,4-trimethyl-4,6-di (2-thienyl)-4*H*-1,3-oxazine-2-amine (3h) Mp = 96 ºC. IR (KBr): *v* = 3082, 2933, 2840, 1652, 1632. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.81 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 5.79 (s, 1H, olefinic), 6.84-7.70 (m, 6H, ArH). MS (EI 70 *eV*) *m/z*: 304 (M^+). Anal. Calcd. for $C_{15}H_{16}N_2OS_2$ (304.43): C, 59.18; H, 5.30; N, 9.20; S, 21.07. Found: C, 59.13; H, 5.22; N, 9.15; S, 20.95.

Data for *N, N*,4-trimethyl-4,6-di (2-naphthyl)-4*H*-1,3-oxazine-2-amine (3i) Mp = 125 ºC. IR (KBr): *v* = 3090, 2946, 2855, 1654, 1635. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H = 1.84 (s, 3H, CH_3), 3.02 (s, 6H, $2CH_3$), 5.81 (s, 1H, olefinic), 6.84-7.70 (m, 14H, ArH). MS (EI 70 *eV*) *m/z*: 392 (M^+). Anal. Calcd. for $C_{27}H_{24}N_2O$ (392.49): C, 82.62; H, 6.16; N, 7.14. Found: C, 82.55; H, 6.10; N, 7.08.

CONCLUSION

The synthesis of a new series of tetrasubstituted 1,3-oxazines in good yields *via* the MCR of dimethyl cyanamide and two moles of aromatic ketones using a binary reagent (TCS/$ZnCl_2$) and methylene chloride as the solvent has been described. The reaction products were characterized by IR, ^{1}H-NMR and ^{13}C NMR spectroscopy, MS and elemental analysis.

REFERENCES

[1] **(a)** B.Ganem; Acc.Chem.Res., **42**, 463 **(2009)**; **(b)** A.Dömling, I.Ugi; Angew.Chem.Int.Ed., **39**, 3168 **(2000)**; **(c)** V.Nair, C.Rajesh, A.U.Vinod, S.Bindu, A.R.Sreekanth, J.S.Mathen, A.L.Balagopal; Acc.Chem.Res., **36**, 899 **(2003)**; **(d)** A.Dömling; Chem.Rev., **106**, 17 **(2006)**; **(e)** J.P.Zhu; Eur.J.Org.Chem., 1133 **(2003)**.

[2] S.M.Kupchan, Y.Komoda, W.A.Court, G.J.Thomas, K.R.M.Smith, A.Karim, C.J.Gilmore, R.C. Haltivanger, R.F.Bryan; J.Am.Chem.Soc., **94**, 1354 **(1972)**.

[3] R.Mueller, Y.X.Li, A.Hampson, S.Zhong, C.Harris, C.Marrs, R.Rachwal, J.Ulas, L.Nielsson, G.Rogers; Bioorg.Med.Chem.Lett., **21**, 3923 **(2011)**.

[4] H.S.Mosher, M.B.Frankel, M.Gregory; J.Am.Chem. Soc., **75**, 5326 **(1953)**.

[5] **(a)** L.Ming, Z.Zujin, T.Wan, L.Ping; Tetrahedron, **68**, 3361 **(2012)**; **(b)** K.Khumtaveeporn, H.Alper; J.Org.Chem., **60**, 8142 **(1995)**; **(c)** H.Cao, H.F.Jiang, C.R.Qi, W.J.Yao, H.J.Chen; Tetrahedron Lett., **50**, 1209 **(2009)**.

[6] D.J.Ramon, M.Yus; Angew.Chem.Int.Ed., **44**, 1602 **(2005)**.

[7] S.Rossi, M.Benaglia, A.Genoni; Tetrahedron, **70**, 2065 **(2014)**.

[8] **(a)** T.K.Khatab, K.A.M.El-Bayouki, W.M.Basyouni; Tetrahedron Lett., **55**, 6039 **(2014)**; **(b)** H.A.Soliman, T.A.Salam; Org.Chem.An Indian Journal, **10**, 63 **(2014)**; **(c)** T.K.Khatab, K.A.M.El-Bayouki, W.M.Basyouni; Tetrahedron Lett., **52**, 1448 **(2011)**; **(e)** D.S.Badawy, E.Abdel-Galil, E.M.Kandeel, K.A.M.El-Bayouki, W.M.Basyouni, T.K.Khatab; Phosphorus, Sulfur, Silicon Relat.Elem., **184**, 220 **(2009)**; **(f)** S.S.Elmorsy, D.S.Badawy, T.K.Khatab; Phosphorus, Sulfur, Silicon Relat.Elem., **181**, 2005 **(2006)**.