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Selectfluor-mediated oxidative methylenation of amide with N,N-dimethylpropanamide for N,N'-methylenebisamide synthesis

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Abstract

A simple and efficient approach for the synthesis of *N,N′*-methylenebisamides through a Selectfluor-mediated oxidative reaction of aromatic amides and *N,N*-dimethylpropanamide (DMP) is described. Remarkable results clearly reveal that DMP plays a dual role in this reaction, as both a one-carbon source and an environment-friendly solvent. Moreover, the process provides new strategies for the synthesis of bisamides with advantages of operationally simple, insensitive to atmospheric conditions and good to high yields.

Keywords: amides; methylenebisamides; selectfluor; DMP; methylene

1 Introduction

Amides and polyamides, the important biological and medicinal scaffolds, have been widely occurred among numerous biologically active compounds, natural products[1], pharmaceuticals, polymers[2] and peptides[3]. In particular, symmetrical *N,N′*-methylenebisamides are critical functional moieties in the formation of peptidomimetic compounds. It has also been reported that these compounds can be used as starting materials for the synthesis of inhibitors against HIV-1 integrases[4]. Among various transformations reported for synthesis of methylenebisamides, the

coupling of aldehydes with various primary amides at acidic conditions is one of the most broadly investigated approaches. Such approaches include using different catalysts such as sulfuric acid[5], triflic acid[6], *p*-toluene sulfonic acid[7], phosphotungstic acid[8] and (SiO_2-PPA)[9]. Extensive researches over past few years have proved that DMSO can be used as the methylene source in organic synthesis[10]. For instance, The synthesis of methylenebisamides can be achieved by using 2,4,6-trichloro[1,3,5]triazine or 2,4-dichloro-6-methoxy[1,3,5]triazine[11], ammonium persulfate[12], or Ni-catalyzed system[13] to activate DMSO. In fact, DMSO acts in these reactions as both methylene source and solvent (Scheme 1).

Recently, a few studies of application of *N*-methylamine compounds as one carbon synthon under transition-metal or oxidant catalyzed conditions have been reported. Li et al. has introduced $Fe_2(CO)_9$ as an efficient catalyst for the preparation of methylene-bridged bis-1,3-dicarbonyl derivatives *via* Fe-catalyzed C-N bond cleavage using *N,N'*-dimethylaniline as the methylene source[14]. In 2012, Zhang et al. reported a Cu(II)-catalyzed, base-switched method for the synthesis of bisindolylmethanes, 3-formylindoles and diaminodiphenylmethanes using tetramethylethylenediamine as methylene and formyl donors under external-oxidant-free conditions[15]. More recently, methylenebisamides were synthesised from amides using $Na_2S_2O_8$/$(NH_4)_2Ce(NO_3)_6$ system in water[16]. Unfortunately, these methods reported for the synthesis of methylenebisamides suffer from drawbacks such as expensive catalyst, corrosive reagent, long reaction time, hazardous organic solvent and low yields. The present work describes the use of Selectfluor™, an exceptionally stable, cheap and user-friendly reagent, as an efficient

oxidant for the synthesis of methylenebisamides. Selectfluor was firstly discovered in 1992[17] and soon after became one of the most popular reagents in one-step reactions to introduce fluorine into organic compounds electrophilically[18-21]. Its thermal stability, low toxicity, good solubility and stability in polar and non-polar solvents such as water, methanol, acetonitrile, nitromethane, tetrahydrofuran and N,N-dimethylformamide are favored by any organic chemistry laboratory[22]. Furthermore, its half-wave potential against saturated calomel electrode (SCE) at 0.33 V leads it to become one of the most powerful oxidants in the N-F fluorinating compounds library[21]. Therefore, selectfluor can be served as an oxidant of many functionalizations of organic compounds other than fluorinations[23-25]. For example, selectfluor can efficiently oxidize amides into imides in the presence of copper(I) bromide[26] and transform indole into 2-oxindole[27]. To explore the C-H/N-H cross-coupling reaction[28,29], herein, we report a new approach for the synthesis of methylenebisamides from primary amides using dimethyl alkylamides as the methylene source oxidized by selectfluor.

2 Results and Discussion

Permutations and combinations of oxidants and their mole ratios at different temperatures provided an optimal reaction condition. At the outset, a model reaction of benzamide **1a** and a methylene source (**2**) was initially investigated at 110°C (Table 1). In the absence of any oxidant the reaction did not proceed at all, indicating that the oxidant is necessary for this transformation (entry 1). In order to select the best oxidant, the reaction was investigated at 110°C for 12h with several oxidants such as *N*-fluorobenzenesulfonimide, DMSO and Selectfluor (entries 2-4). To

our delight, selectfluor has showed the best oxidative activity amongst the oxidants examined and 91% yield of the methylenebisamide **3a** was obtained (entry 4). However, with a decrease of reaction temperature, the yield of **3a** was correspondingly decreased (entry 5) and the reaction was not proceed at 50°C and room temperature, respectively (entries 6-7). On the other hand, further increase of the reaction temperature to 130°C did not enhance the reaction selectivity and only 81% of the product yield was achieved (entry 8). Therefore, 110°C is an optimal temperature to process the reaction. The amount of selectfluor was also investigated. When catalytic amounts of selectfluor were applied (0.1 equiv. and 0.5 equiv., respectively), lower product yields were achieved compared to that by an equal amount of selectfluor (entries 9-10). On the other side, when 1.5 equiv. amount of selectfluor was applied for this oxidation reaction, a slightly lower yield was found, indicating that it may promote a further oxidation of the resulting product and lead to lower yield (entry 11). Various methylene donors have also been examined and it was found that when the reaction was carried out in *N,N'*-dimethylformamide (entry 12), *N,N'* -dimethylacetamide (entry 13), DMSO (entry 14) or formaldehyde (entry 15) it was not as efficient as that in *N,N'*-dimethylpropanamide (DMP). Interestingly, when N-methylacetamide was investigated as the methylene donor, the reaction failed (entry 16). Although N-methylamine compounds such as tetramethylethylenediamine and *N,N'*-dimethylaniline have been reported to provide the methylene synthon[30, 31], the reaction did not proceed at all using selectfluor as the oxidant (entries 17-18). Therefore, the standard reaction conditions were built using benzamide (1.0 equiv.), selectfluor (1.0 equiv.) and DMP (4 mL) at 110°C under air for 12h.

With the optimized conditions in hand, we decided to explore the substrate scope for aromatic amide containing both electron-donating and electron-withdrawing groups. The obtained outcomes are summarized in Table 2. Aromatic amines carrying an electron-donating group (CH_3-, CH_3O-) at *ortho*-, *meta*- or *para*- position reacted efficiently to acquire the corresponding bisamides without significant different yields (85-92%) (entries 2, 3, 8, 11 and 12). In contrast, the benzamides substituted with an electron-withdrawing group such as *p*-F, *p*-Cl, *m*-F, *o*-F furnished the corresponding bisamides in slightly lower yields (78-88%) (entries 4, 5, 9 and 13). Surprisingly, only 25% yield was achieved when *o*-chlorobenzamide was used as the reactant (entry 14). Furthermore, similar product yields were obtained from *p*-NO_2 and *m*-NO_2 substituted benzamides (entries 6 and 10). This phenomenon indicates that under such protocol the reactivity of aromatic amides containing an electron-withdrawing group is lower than that with an electron-donating group. Unfortunately, 4-hydroxybenzamide remained unreactive, which may be due to an interference of an active proton on the ring (entry 7). The bisamide **3o** was obtained in high yield from 2-naphthamide, similar to that of unsubstituted benzamide (entry 15). Interestingly, When di-substituted benzamides were examined as the reactants under same conditions (entries 16-19), only 2,5-difluorobenzamide can be transformed into the corresponding bisamide **3r** in a low yield (17%). Moreover, when 3,5-dimethoxy substituted analogue (**1u**) was carried out under same conditions, the desired bisamide was not obtained. Instead, a fluorine atom was introduced into the aromatic ring to afford **4** with a medium yield (Scheme 2). Apart from aromatic amides, 2-phenylacetamide can afford the corresponding bisamide **3t** under same conditions in a good yield (entry 20). However, other aliphatic amides such as acetamide, and

propionamide remain unreactive. In addition, N-methylbenzamide, 2-picolinamide, 2-thiophenecarboxamide, benzothioamide and p-toluenesulfonamide were also investigated for the reaction but failed. It is noteworthy that when phthalamide was used as the reactant, only phthalimide (**5**) was afforded in a good yield under such protocol.

A plausible mechanism has been depicted in Scheme 4 based on literature reports[32,33]. Firstly the nitrogen atom of DMP was fluorinated by selectfluor to form an onium ion **A**, followed by removal of one molecule of HF to produce iminium ion **B**. The intermediate **B** was nucleophilically attacked by the aromatic amide to obtain intermediate **C**. Intermediate **C** was nucleophilically attacked again by another molecule of aromatic amide to afford the final desired bisamide **3**.

3 Conclusion

In conclusion, we have developed a convenient approach to methylenebisamides through a selectfluor-mediated oxidation reaction of aromatic amides and DMP. The substrates are easily available and the method is simple and avoids the use of formaldehyde, transition-metals or strong acid catalysts. The methylenebisamides are obtained in good to high yields. Further study of the oxidation of selectfluor in organic synthesis is currently underway.

4 Experimental

All the chemical reagents used in the synthesis were of research grade and were obtained from commercial sources. All the reactions were monitored by thin-layer chromatography (TLC). All

target products were characterized by using NMR (BrukerAvance 600 spectrometer) with TMS as the internal standard in DMSO or $CDCl_3$ and High resolution mass spectra (MicroMass Q-TOF instrument). The chemical shifts are reported in parts per million (ppm), the coupling constants (J) are expressed in hertz (HZ). IR spectra are recorded as KBr pellets on a Nicolet IS50 infrared spectrometer. Melting points are determined using an WRS-1B apparatus and are uncorrected.

General procedure for the preparation ofmethylenebisamides: a mixture of acylamide (1 mmol) and selectfluor (1 mmol) was stirred in DMP (4 mL) at 110°C. After the completion of the reaction as determined by TLC (Petroleum ether-ethyl acetate, 1:2), the mixture was cooled to room temperature. Water (20 ml) was added and the mixture was extracted with EtOAc (3×20 ml). The organic layer was separated and dried over Na_2SO_4. Removal of the solvents produced a residue which was purified using column chromatography, eluted with a mixture of EtOAc/petroleum ether (1:1, v/v), to afford the pure symmetrical methylenebisamides.

***N,N′*-methylenedibenzamide (3a)**: White solid; yield: 115mg (91%); mp 217-218°C (lit[34]. mp 216-217°C).IR (ATR): 3308, 2924, 1634,1577, 1527, 1288, 693 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$):δ7.81 (d, J = 7.3 Hz, 4H, ArH), 7.56-7.48 (m, 4H, ArH, NH), 7.43 (m, 4H, ArH), 5.06 (t, J = 6.2 Hz, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ166.91, 134.40, 131.86, 128.71, 127.88, 45.63. ESI-MS: $(M+Na)^+$ 277.

***N,N′*-methylenebis(4-methylbenzamide) (3b)**:White solid; yield: 120mg (85%); mp 211-214°C (lit[13]. mp 212-214°C). IR (ATR): 3311, 2967, 2918, 1635, 1530, 1505, 1284, 1110, 757 cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ7.71-7.76 (d, 4 H, ArH), 7.48 (t, J = 6.7Hz, 2H, NH), 7.24-7.21 (m, 4

H, ArH), 5.01 (t, J = 6.4 Hz, 2H, CH_2), 2.39 (s, 6H, CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ168.38, 142.55, 130.60, 129.29, 127.18, 45.52, 21.50. ESI-MS: $(M+Na)^+$ 305.

***N,N′*-methylenebis(4-methoxybenzamide) (3c)**: White solid; yield: 143mg (85%); mp 212-213°C (lit[34]. mp 223-224°C). IR (ATR): 3325, 2965, 2920, 1632, 1505, 1293, 1251, 1185, 1114, 1034, 846, 769 cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85-7.74 (d, 4 H, ArH), 7.51 (t, J = 6.3Hz, 2H, NH), 6.95-6.88 (m, 4 H, ArH), 5.00 (t, J = 6.4 Hz, 2H, CH_2), 3.84 (s, 6H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 168.00, 162.57, 129.10, 125.73, 113.79, 55.43, 45.59. ESI-MS: $(M+H)^+$ 315.

***N,N′*-methylenebis(4-fluorobenzamide) (3d)**: White solid; yield: 121mg (83%); mp 227-228°C (lit[16]. mp 223-224°C). IR (ATR): 3358, 3075, 1646, 1500, 1285, 1239, 850, 767 cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84-7.81 (d, 4 H, ArH), 7.69 (t, J = 6.5Hz, 2H, NH), 7.13-7.09 (m, 4 H, ArH), 5.00 (t, J = 6.3 Hz, 2H, CH_2). ^{13}C NMR (151 MHz, $CDCl_3$): δ 167.55, 131.54, 129.76, 128.89, 115.84, 45.75. ESI-MS: $(M+Na)^+$ 313.

***N,N′*-methylenebis(4-chlorobenzamide) (3e)**: White solid; yield: 143mg (88%); mp 245-246°C (lit[13]. mp 245-247°C). IR (ATR): 3317, 3179, 3051, 1643, 1526, 1406, 1302, 1093, 847, 789 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 9.17 (t, J = 5.6 Hz, 2H, NH), 7.92 (d, J = 8.1 Hz, 4H, ArH), 7.54 (d, J = 8.1 Hz, 4H, ArH), 4.85 (t, J = 5.6 Hz, 2H, CH_2). ^{13}C NMR (151 MHz, DMSO-d_6): δ 165.92, 136.72, 133.14, 129.85, 128.83, 45.65. ESI-MS: $(M+Na)^+$ 345.

***N,N′*-methylenebis(4-nitrobenzamide) (3f)**: White solid; yield: 53mg (31%); mp 235-237°C (lit[34]. mp 234-235°C).IR (ATR): 3294, 1643, 1600, 1536, 1516, 1351, 1289, 1116, 724 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 8.8 Hz, 4H, ArH), 7.98 (d, *J* = 8.8 Hz, 4H, ArH), 7.67 (brs, 2H, NH,), 5.06 (t, *J* = 6.0 Hz, 2H, CH_2).^{13}C NMR (126 MHz, DMSO-d_6): δ 165.40, 149.62, 139.98, 129.46, 123.97, 45.85. ESI-MS: $(M+Na)^+$ 367.

***N,N′*-methylenebis(3-methoxybenzamide) (3h)**: White solid; yield: 123mg (87%); mp 153-154°C (lit[34]. mp165-166°C). IR (ATR): 3239, 3069, 2971, 2944, 1642, 1529, 1491, 1306, 1240, 1107, 873, 738, 714 cm^{-1}.^1H NMR (600 MHz, DMSO-d_6): δ δ 9.06 (t, *J* = 5.7 Hz, 2H, NH), 7.50 – 7.45 (m, 4H, ArH), 7.37 (t, *J* = 7.9 Hz, 2H, ArH), 7.11 – 7.07 (m, 2H, ArH), 4.85 (t, *J* = 5.6 Hz, 2H, CH_2), 3.80 (s, 6H, OCH_3). ^{13}C NMR (126 MHz, DMSO-d_6): δ 166.64, 159.59, 135.82, 129.85, 120.19, 117.86, 112.88, 55.74, 45.62. ESI-MS: $(M+H)^+$315.

***N,N′*-methylenebis(3-fluorobenzamide) (3i)**:White solid; yield: 113mg (78%); mp 216-218°C (lit[13]. mp 222-224°C). IR (ATR): 3300, 3071, 1635, 1533, 1306, 1220, 1110, 765 cm^{-1}.^1H NMR (500 MHz, DMSO-d_6): δ 9.18 (t, *J* = 5.6 Hz, 2H, NH), 7.77 (d, *J* = 10.1, 2.0 Hz, 2H, ArH), 7.71 (dt, *J* = 10.1, 2.7, 1.6 Hz, 2H, ArH), 7.53 (m, *J* = 8.0, 5.9 Hz, 2H, ArH), 7.39 (t, *J* = 8.5, 2.7, 1.0 Hz, 2H, ArH), 4.86 (t, *J* = 5.6 Hz, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d_6): δ 165.61, 162.35, 136.73, 130.95, 124.09, 118.86, 114.67, 45.70. ESI-MS: $(M+Na)^+$ 313.

***N,N′*-methylenebis(3-nitrobenzamide) (3j)**: White solid; yield: 46mg (27%); mp 227-229°C (lit[34]. mp225-226°C).IR (ATR): 3300, 3065, 1640, 1524, 1350, 1116, 728 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.59 (t, *J* = 6.0 Hz, 2H, NH), 8.75 (d, *J* = 2.2 Hz, 2H, ArH), 8.44 – 8.34 (m,

4H, ArH), 7.79 (dt, *J* = 6.0 Hz, 2H, ArH), 4.92 (td, *J* = 5.6, 2.1 Hz, 2H, CH_2).^{13}C NMR (126 MHz, DMSO-d_6): δ 164.95, 148.23, 135.78, 134.38, 130.62, 126.57, 122.70, 45.97. ESI-MS: $(M+Na)^+$ 367.

***N,N′*-methylenebis(2-methoxybenzamide) (3k)**: White solid; yield: 145mg (92%); mp 157-159°C. IR (ATR): 3387, 2976, 2944, 1644, 1538, 1485, 1302, 1244, 1012, 751 cm^{-1}.^{1}H NMR (600 MHz, DMSO-d_6): δ 8.87 (t, *J* = 5.8 Hz, 2H, NH), 7.86 (dd, *J* = 7.7, 1.9 Hz, 2H, ArH), 7.50 (m, 2H, ArH), 7.16 (d, *J* = 8.3 Hz, 2H, ArH), 7.05 (dt, *J* = 7.6, 1.0 Hz, 2H, ArH), 4.87 (t, *J* = 5.8 Hz, 2H, CH_2), 3.90 (s, 6H, OCH_3).^{13}C NMR (126 MHz, DMSO-d_6): δ 165.53, 157.72, 133.34, 131.27, 122.19, 121.09, 112.67, 56.47, 45.52. ESI-MS: $(M+Na)^+$ 337.

***N,N′*-methylenebis(2-methylbenzamide) (3l)**: White solid; yield: 120mg (85%); mp 185-186°C (lit[13]. mp 204-206°C). IR (ATR): 3293, 2963, 2924, 1639, 1529, 1395, 1304, 1283, 1118, 746, 700 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (t, *J* = 5.7 Hz, 2H, NH), 7.36 – 7.31 (m, 4H, ArH), 7.22 (m, 4H, ArH), 4.76 (t, *J* = 5.7 Hz, 2H, CH_2), 2.35 (s, 6H, CH_3).^{13}C NMR (126 MHz, DMSO-d_6): δ 169.70, 137.11, 135.75, 130.85, 129.82, 127.65, 125.86, 44.90, 19.84. ESI-MS: $(M+Na)^+$ 305.

***N,N′*-methylenebis(2-fluorobenzamide) (3m)**: White solid; yield: 115mg (79%); mp 188-189°C (lit[34]. mp192-193°C).IR (ATR): 3293, 3069, 1640, 1529, 1306, 1222, 1116, 755 cm^{-1}.^{1}H NMR (600 MHz, DMSO-d_6): δ 8.90 (t, *J* = 6.1, Hz, 2H, NH), 7.64 (dt, *J* = 7.6, 1.8 Hz, 2H, ArH), 7.56-7.52 (m , 2H, ArH), 7.31 – 7.26 (m, 4H, ArH), 4.81 (t, *J* = 6.1 Hz, 2H, CH_2).^{13}C NMR (126

MHz, DMSO-d_6): δ 164.45, 160.74, 133.17, 130.64, 124.91, 123.87, 116.61, 45.22. ESI-MS: $(M+Na)^+$ 313.

***N,N′*-methylenebis(2-chlorobenzamide) (3n)**: White solid; yield: 41mg (25%); mp 185-187°C (lit[13]. mp189-190°C).IR (ATR): 3283, 3053, 1644, 1529, 1393, 1301, 1111, 751 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 7.63 (d, J = 7.6, Hz, 2H, ArH), 7.43 – 7.32 (m, 8H, NH, ArH), 5.03 (t, J = 6.3 Hz, 2H, CH_2).^{13}C NMR (126 MHz, DMSO-d_6): δ 168.60, 136.83, 131.00, 130.06, 129.44, 129.11, 127.46, 44.74. ESI-MS: $(M+Na)^+$ 345.

***N,N′*-methylenebis(2-naphthamide) (3o)**: White solid; yield: 154mg (87%); mp 238-239°C (lit[12]. mp 235-237°C).IR (ATR): 3299, 3272, 3061, 1641, 1534, 1302, 1114, 781 cm^{-1}.^{1}H NMR (600 MHz, DMSO-d_6): δ 9.29 (t, J = 5.7 Hz, 2H, NH), 8.56 (d, J = 1.5 Hz, 2H, ArH), 8.04 – 7.96 (m, 8H, ArH), 7.64-7.57 (m, 4H, ArH), 4.99 (t, J = 5.6 Hz, 2H, CH_2).^{13}C NMR (126 MHz, DMSO-d_6): δ 167.00, 134.69, 132.57, 131.74, 129.36, 128.31, 128.30, 128.16, 128.07, 127.20, 124.75, 45.78. ESI-MS: $(M+Na)^+$ 377.

***N,N′*-methylenebis(2,5-difluorobenzamide) (3r)**: White solid; yield: 28mg (17%); mp 200-201°C.IR (ATR): 3330, 2933, 2676, 2489, 1640, 1534, 1283, 1187, 820 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (t, J = 5.8 Hz, 2H, NH), 7.45 – 7.34 (m, 6H, ArH), 4.79 (t, J = 5.8 Hz, 2H, CH_2).^{13}C NMR (151 MHz, DMSO-d_6): δ 163.31, 119.73, 119.56, 118.63, 118.45, 116.81, 116.64, 45.24. HRMS calcd for $C_{15}H_{10}F_4N_2O_2Na^+$ 349.0571, found 349.0559.

***N,N′*-methylenebis(2-phenylacetamide) (3t)**: White solid; yield: 103mg (73%); mp 208-209°C (lit[13]. mp 213-215°C).IR (ATR): 3305, 3065, 1643, 1537, 1391, 1246, 1114, 697 cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (t, J = 6.0 Hz, 2H, NH), 7.29 – 7.26 (m, 4H, ArH), 7.25 – 7.21 (m, 6H, ArH), 4.38 (t, J = 6.0 Hz, 2H, CH_2), 3.41 (s, 4H, $COCH_2$).^{13}C NMR (151 MHz, DMSO-d_6): δ 171.08, 136.63, 129.46, 128.61, 126.78, 43.82, 42.44. ESI-MS: $(M+H)^+$ 283.

2-fluoro-3,5-dimethoxybenzamide (4): White solid; yield: 108mg (53%); mp 121-122°C.

IR (ATR): 3383, 3192, 3016, 1655, 1595, 1406, 1213, 1159, 785 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (dd, J = 5.1, 3.1 Hz, 1H, ArH), 6.69 (dd, J = 7.2, 3.1 Hz, 1H, ArH), 5.85 (s, 2H, NH), 3.89 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.86, 155.67, 148.59, 146.70, 105.43, 105.38, 103.59, 56.50, 55.89. HRMS calcd for $C_9H_{11}FNO_3^+$200.0717, found 200.0711.

Isoindoline-1,3-dione (5): White solid; yield: 113mg (77%); mp 235-236°C. (lit[34]. mp 236-238°C). IR (ATR): 3197, 3051, 1743, 1599, 1380,1307cm^{-1}.^{1}H NMR (500 MHz, DMSO-d_6): δ 11.35 (s, 1H, NH), 7.83 (s, 4H, ArH).^{13}C NMR (151 MHz, DMSO-d_6): δ 169.68, 134.77, 133.06, 123.39. ESI-MS: $(M+H)^+$ 148.

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Scheme 1 Traditional routes to methylenebisamides

Scheme 2 Reaction using 3,5-dimethoxybenzamide as the starting material

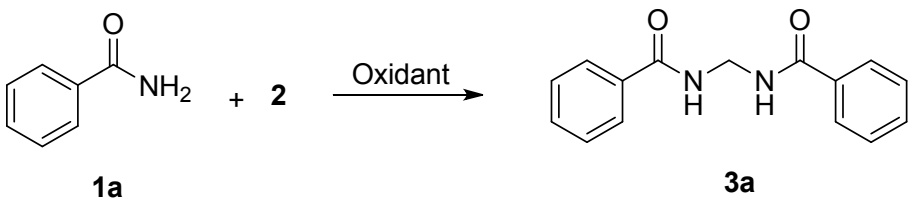
Scheme 3 Reaction using phthalamide as the starting material

Scheme 4 A plausible mechanism for synthesis of bisamides

Table 1 Optimization of the reaction conditions[a]

Table 2 Scope of the substrates [a]

Table 1 Optimization of the reaction conditions[a]



1a **3a**

Entry	2	Oxidant	Equiv.	Temp./°C	Yield/%[b]
1	$EtCONMe_2$	-	-	110	NR
2	$EtCONMe_2$	NFSI	1.0	110	48
3	$EtCONMe_2$	DMSO	1.0	110	23
4	$EtCONMe_2$	Selectfluor	1.0	110	91
5	$EtCONMe_2$	Selectfluor	1.0	80	83
7	$EtCONMe_2$	Selectfluor	1.0	r.t.	NR
8	$EtCONMe_2$	Selectfluor	1.0	130	81
9	$EtCONMe_2$	Selectfluor	0.1	110	25
10	$EtCONMe_2$	Selectfluor	0.5	110	40
11	$EtCONMe_2$	Selectfluor	1.5	110	86
12	$HCONMe_2$	Selectfluor	1.0	110	53

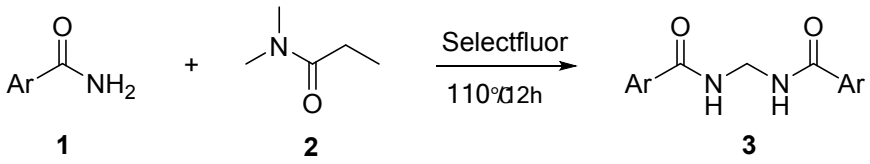
13	$MeCONMe_2$	Selectfluor	1.0	110	75
14	DMSO	Selectfluor	1.0	110	83
15	HCHO	Selectfluor	1.0	110	72
16	MeCONHMe	Selectfluor	1.0	110	NR
17	$Me_2NCH_2CH_2NMe_2$	Selectfluor	1.0	110	NR
18	$PhNMe_2$	Selectfluor	1.0	110	NR

[a]Reaction conditions: **1a** (1.0 mmol) and **2** (4 mL) with certain amount of oxidant at the indicated temperature under air for 12h.

[b]Isolated yields.

NR, no reaction.

Table 2 Scope of the substrates [a]



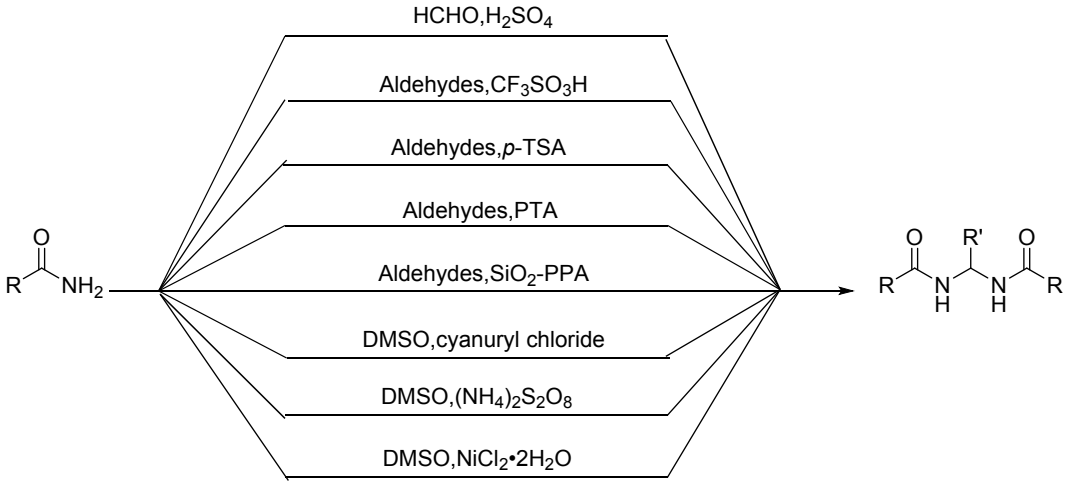
Entry	Substrate	Product	Yield/%[b]	Entry	Substrate	Product	Yield/%[b]
1	Ph	**3a**	91	**11**	2-$MeOC_6H_4$	**3k**	92
2	4-MeC_6H_4	**3b**	85	**12**	2-MeC_6H_4	**3l**	85
3	4-$MeOC_6H_4$	**3c**	91	**13**	2-FC_6H_4	**3m**	79
4	4-FC_6H_4	**3d**	83	**14**	2-ClC_6H_4	**3n**	25
5	4-ClC_6H_4	**3e**	88	**15**	2-naphthyl	**3o**	87
6	4-$NO_2C_6H_4$	**3f**	31	**16**	2,6-$Me_2C_6H_3$	**3p**	0
7	4-OHC_6H_4	**3g**	0	**17**	2,6-$F_2C_6H_3$	**3q**	0
8	3-$MeOC_6H_4$	**3h**	87	**18**	2,5-$F_2C_6H_3$	**3r**	17
9	3-FC_6H_4	**3i**	78	**19**	3,5-$(CF_3)_2C_6H_3$	**3s**	0

10	3-$NO_2C_6H_4$	**3j**	27	**20**	$C_6H_5CH_2$	**3t**	73

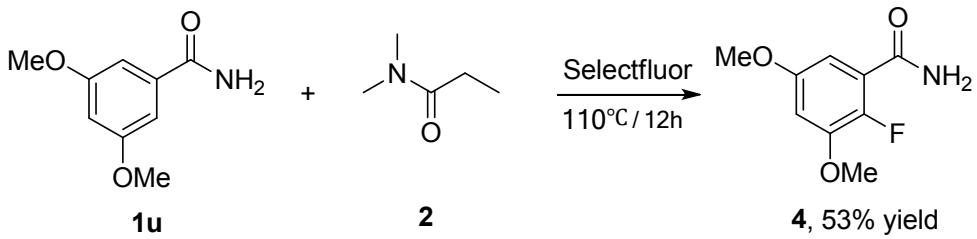
[a]Reaction conditions: aromatic amide (1 mmol),Selectfluor (1 mmol),DMP (4 mmol).

[b] Isolated yields.

Scheme 1 Traditional routes to methylenebisamides

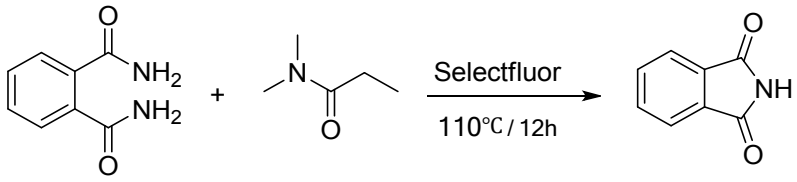


Scheme 2 Reaction using 3,5-dimethoxybenzamide as the starting material



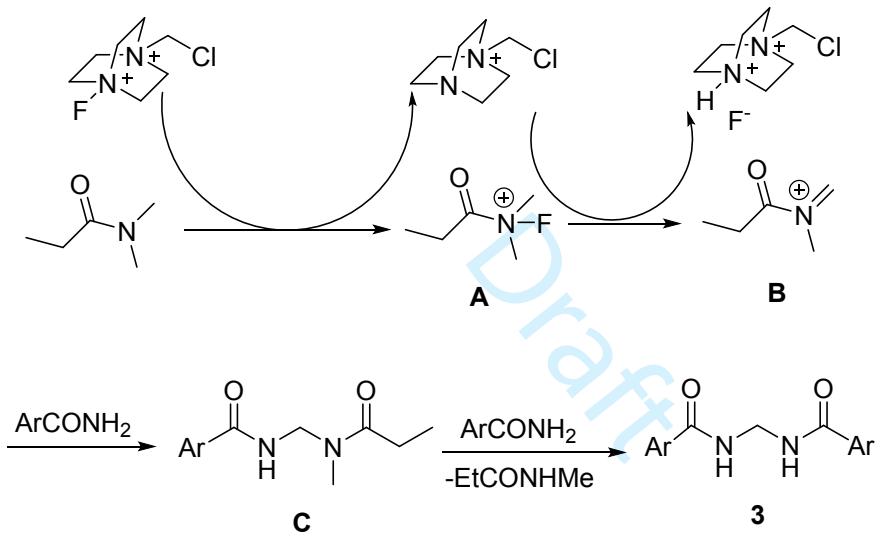
1u **2** **4**, 53% yield

Scheme 3 Reaction using phthalamide as the starting material



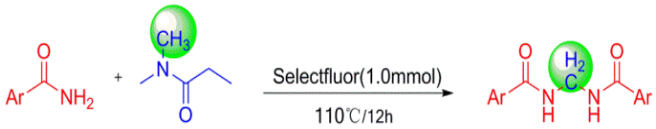
1v **2** **5**, 77% yield

Scheme 4 A plausible mechanism for synthesis of bisamides



Graphical Abstract

Selectfluor-mediated oxidative methylenation of amide with N,N-dimethylpropanamide for methylenebisamide synthesis



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