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SYNTHESIS OF FURAZANE CONJUGATED NEW HETEROCYCLES

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Abstract- An improved route for the synthesis of 3-(4-aminofurazane-3-yl)-1,2,4-oxadiazole heterocycles using micro-wave irradiation is reported. The preparation of novel 4-(thiazol-4-yl)furazan-3-ylamine, 4-(pyrimidin-4-yl)furazan-3-ylamine and, 4-(pyrazolidin-3-yl)furazan-3-ylamine heterocycles are described.

Furazanes (1,2,5-oxadiazoles) have been reported to exhibit a wide spectrum of biological properties.[1] In particular, agrochemical applications of furazanes and their derivatives as herbicides, plant-growth regulators and pesticides have been described.[2] Our biological screening revealed that 3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]oxadiazol-5-one (**5**) exhibits herbicidal activity on broad leaf (*dicotyledones*) weeds. This prompted us to investigate the synthesis of novel 4-aminofurazane heterocycles.

In the first part of this communication we report the preparation of **5** as well as a new and efficient method for the high speed synthesis of [3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]oxadiazol-5-yl]amine derivatives (**4**).

In the second part, we report the preparation of novel 4-aminofurazane rings conjugated to thiazole, pyrimidine and pyrazolidine heterocycles.

Few examples have been reported in the literature describing the synthesis of 3-(4-aminofurazan-3-yl)-[1,2,4]oxadiazole heterocycles.[3] 4-(5-Trichloromethyl[1,2,4]oxadiazol-3-yl)-furazan-3-ylamine (**3)** appeared to be the intermediate of choice for the preparation of both 3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]oxadiazol-5-one (**5**) and new [3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]oxadiazol-5-yl]amine derivatives (**4a-p**) (Scheme 1). Indeed, it has been reported that the trichloromethyl group at the C-5 position of a 1,2,4-oxadiazole ring can be readily substituted by nucleophiles such as guanidines to yield 5-amino-1,2,4-oxadiazole derivatives.[4]

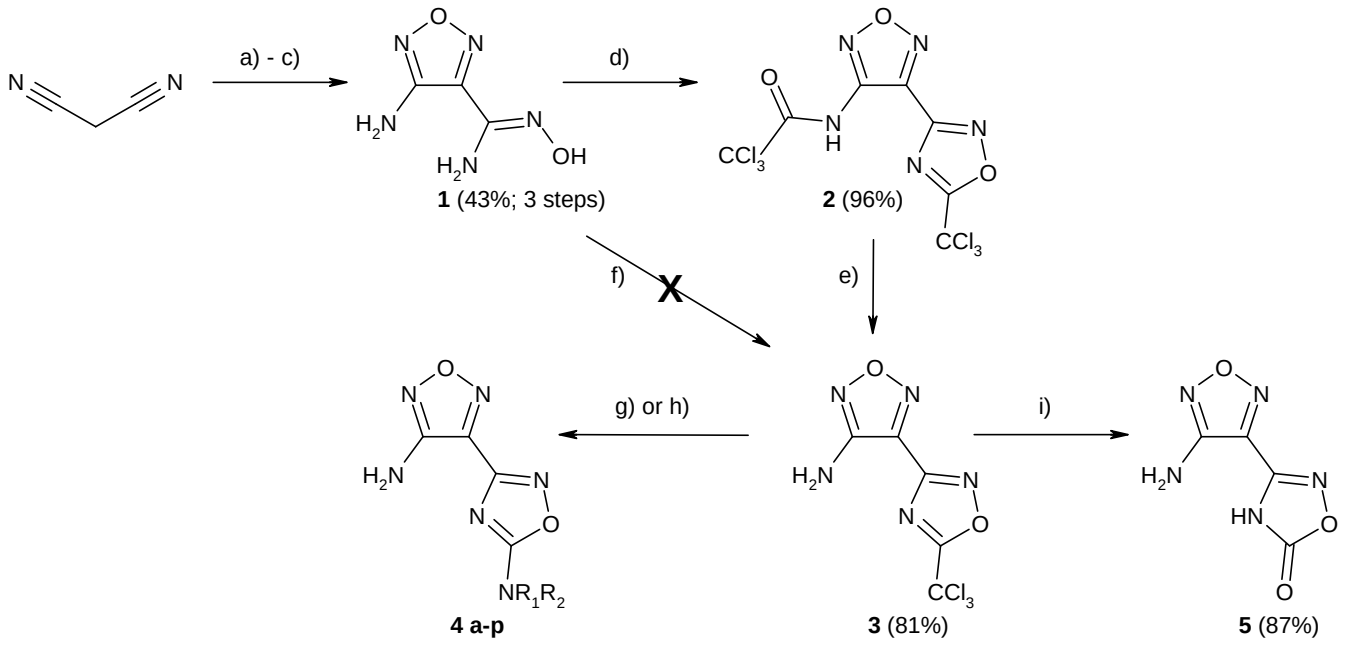
The sequence followed for the preparation of the amide oxime (**3**) is similar to the one previously published by Andrianov *et al.*[3d] However, their one-pot procedure for the preparation of **3** directly from **1**[5] could not be reproduced in our hands (lit.,[3d] 58%). Our new stepwise pathway involves intermediate (**2**) and provides **3** more efficiently from **1** (77% yield two steps).

Treatment with *p*-toluidine was required for the selective removal of the trichloroacetyl group of the intermediate (**2**) which provides **3** in 81% yield. The ammonolysis of **3** in the presence of NH_4OH gave **5** (87% yield).

In order to access a number of structurally diverse analogs of **5**, a small library was prepared by treating **3** with a series of both primary and secondary amines. When the reaction was performed in EtOH/THF at 70°C (method A), the reaction was slow (2-3 days) and low yielding, but nonetheless provided a number of pure [3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]oxadiazol-5-yl]amines after crystallisation.

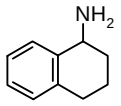
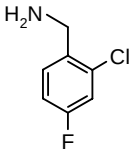
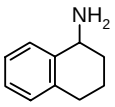
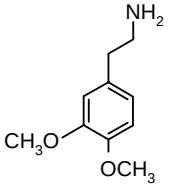
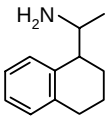
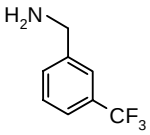
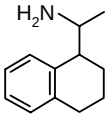
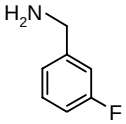
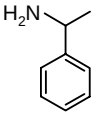
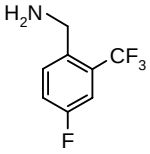
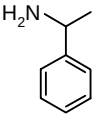
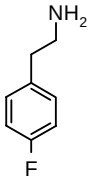
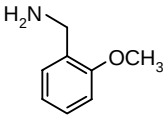
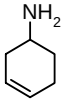
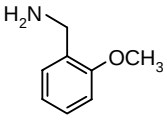
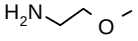
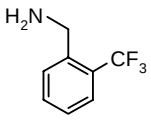
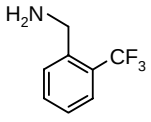
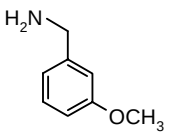
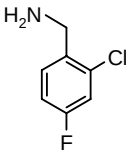
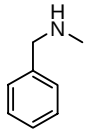
The efficiency of the process could be drastically improved when **3** and 1.2 eq. of amine were adsorbed together on neutral alumina and irradiated in the microwave oven at 400 W (method B). Under these conditions, the reactions were much faster (< 20 min) and substantially cleaner.

The compounds prepared by these two methods are summarized in Table 1.

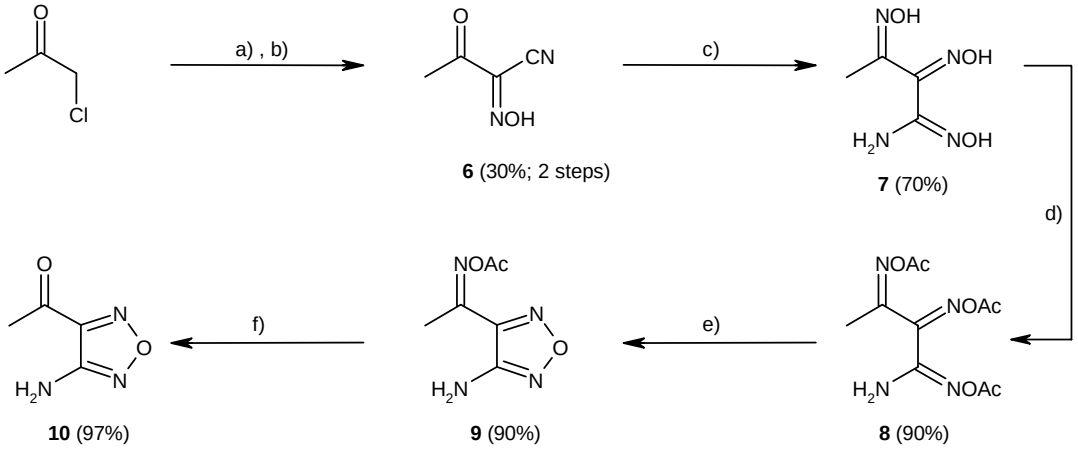


Scheme 1. a) $NaNO_2$ (2 eq.), HCl (2N), rt, 5 h; b) $NH_2OH.HCl$ (2.2 eq.), NaOH (pH=10), rt; c) reflux, 3 h; d) $(CCl_3CO)_2O$, 120°C, 5 h; e) *p*-toluidine (2 eq.), C_2H_5OH, 80°C, 19 h; f) $(CCl_3CO)_2O$, 60-80°C (lit.,[2d] 58%); g) **method A** : amine (3-5 eq.), C_2H_5OH, 70°C, 2-3 d.; h) **method B** : amine (1.2 eq.) on neutral alumina, microwave (400W), 2x10 min.; i) 25% NH_4OH.

Table 1. Transformation of **3** into **4**

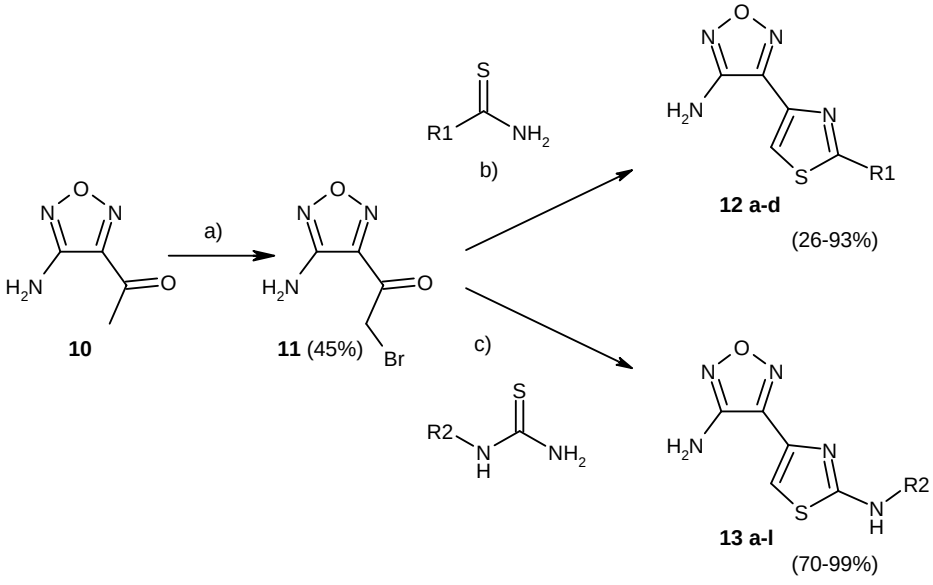
entry	amine	method	product	yield	entry	amine	method	product	yield
1		A	**4a**	<5%	12		B	**4f**	90%
2		B	**4a**	quant.	13		A	**4g**	44%
3		A	**4b**	15%	14		A	**4h**	81%
4		B	**4b**	quant.	15		A	**4i**	90%
5		A	**4c**	65%	16		A	**4j**	88%
6		B	**4c**	95%	17		A	**4k**	79%
7		A	**4d**	30%	18		A	**4l**	43%
8		B	**4d**	88%	19		A	**4m**	57%
9		A	**4e**	33%	20		A	**4n**	70%
10		B	**4e**	86%	21		B	**4o**	96%
11		A	**4f**	39%	22		A	**4p**	36%

We also report the preparation of novel 4-aminofurazanes bearing 5- or 6- membered ring heterocycles.[6] Their syntheses use 1-(4-aminofurazan-3-yl)ethanone (**10**)[7,8] as a key intermediate (Schemes 3 and 4). It has been reported that such 3-acylated furazane rings can be prepared through the reduction of the corresponding carbonyl-substituted furoxans.[7] We report here a new synthesis of **10** as depicted in Scheme 2 in which the key step is the mild and regioselective cyclisation of **8** induced by the treatment with NaOAc in dioxane at 60°C, to give **9** in high yield.



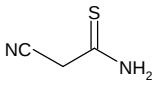
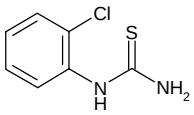
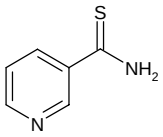
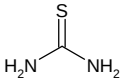
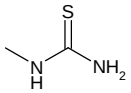
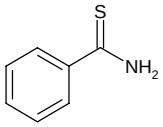
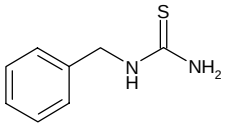
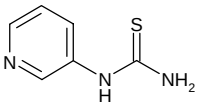
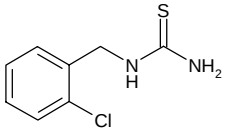
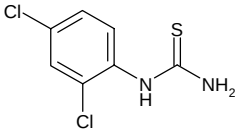
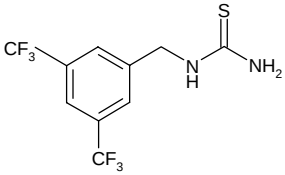
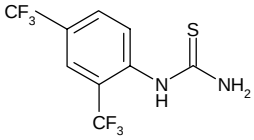
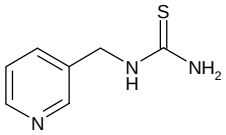
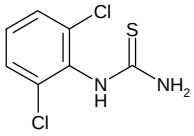
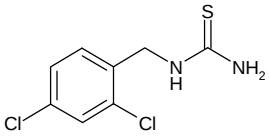
Scheme 2. a) isopentyl nitrite, $(C_2H_5)_2O$, HCl; b) KCN (1.8 eq.), $(C_2H_5)_2O$, H_2O, 45°C ; c) $H_2NOH.HCl$, NaOH, H_2O, rt ; d) Ac_2O, O°C-rt ; e) NaOAc (4 eq.), dioxane, 60°C; f) 20% HCl, H_2O, reflux, steam distillation.

1-(4-Aminofurazan-3-yl)ethanone (**10**) was brominated according to reported conditions.[8b] Thiazole derivatives (**12** and **13)** were prepared in 26 to 99% yields through the Hantzsch reaction of bromide (**11**)[8b] and the corresponding thioamides or thioureas (Scheme 3 and Table 2).[9]



Scheme 3. a) Br_2 (1.05 eq.), AcOH (100%), 55°C; b) **method A**: 1.1 eq. nucleophile, benzene, reflux, 2-3 h, Dean-Stark; c) **method B**: 1.1 eq. nucleophile, C_2H_5OH, reflux, 2-3 h.

Table 2. **Synthesis of 4-(thiazol-4-yl)furazan-3-ylamine derivatives (12) and (13)**

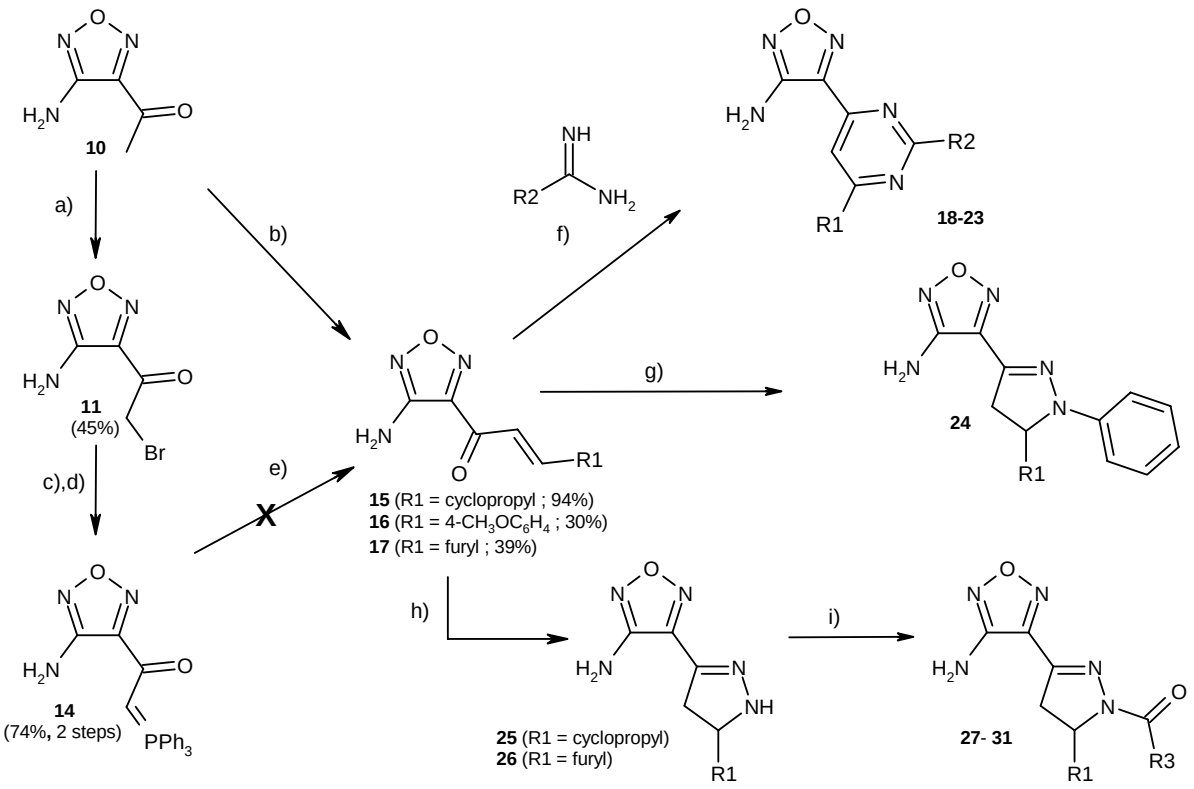
entry	reagent	product	yield	entry	reagent	product	yield
1		**12a**	60%	9		**13e**	70%
2		**12b**	26%	10		**13f**	79%
3		**12c**	34%	11		**13g**	91%
4		**12d**	93%	12		**13h**	98%
5		**13a**	87%	13		**13i**	94%
6		**13b**	75%	14		**13j**	85%
7		**13c**	99%	15		**13k**	90%
8		**13d**	88%	16		**13l**	96%

4-(Pyrimidin-4-yl)furazan-3-ylamine and 4-(pyrazolidin-3-yl)furazan-3-ylamine heterocycles (**18-23** and **24** to **31**) respectively are available in three steps from **10** *via* the reaction of **15** with ambident nucleophiles such as amidines, guanidines or hydrazines (Scheme 4 and Table 3).

As shown in the Scheme 4, triphenylphosphorane (**14**) did not react with aldehydes and only starting materials were recovered. In contrast, piperidine catalyzed aldol condensations between **10** and various aldehydes proceeded in satisfactory to excellent yields (Scheme 4).

The resulting α,β-unsaturated ketones (**15**, **16**, and **17**) were allowed to react with amidines and guanidines in the presence of oxygen to give 4-(pyrimidin-4-yl)furazan-3-ylamine derivatives (**24** to **31**) in low to moderate yields. Compounds (**15** and **17**) underwent reaction with hydrazine to give oxygen sensitive

4-(pyrazolidin-3-yl)furazan-3-ylamine heterocycles which were directly acylated with various acid chlorides in good yields, thus allowing the introduction of additional points of diversity.



Scheme 4. a) Br_2 (1.05 eq.), AcOH (100%), 55°C; b) R^1CHO (2.0 eq.), piperidine (0.1 eq.), C_2H_5OH /THF: 5/1, 50°C; c) PPh_3 (1.0 eq.), toluene, 100°C; d) NaOH (2N), CH_3OH, 0°C; e) R^1CHO (1.2 eq.), piperidine (0.1 eq.), 60°C; f) amidine or guanidine (1.1 eq.), *N*,*N*-dimethylacetamide, 60°C, O_2 (gas); g) $PhNHNH_2$ (2.0 eq.), THF/ C_2H_5OH: 1/20, rt; h) $H_2NNH_2.H_2O$ (10 eq.), THF, rt; i) R^3COCl (1.2 eq.), pyridine (3.0 eq.), CH_2Cl_2, rt.

Table 3. **Synthesis of compounds (18 to 31)**

entry	educt	R1	R2	product	yield	entry	educt	R1	R3	product	yield
1*	**15**	cyclopropyl	methyl	**18**	29%	8	**15**	cyclopropyl		**25**	92%
2	**15**	cyclopropyl	*p*-methoxyphenyl	**19**	14%	9	**17**	2-furyl		**26**	99%
3	**15**	cyclopropyl	phenyl	**20**	26%	10	**25**	cyclopropyl	methyl	**27**	74%
4	**15**	cyclopropyl	aniline	**21**	16%	11	**26**	2-furyl	2,4-dichlorophenyl	**28**	92%
5	**15**	cyclopropyl	benzylamine	**22**	25%	12	**26**	2-furyl	(4-chlorophenoxy)methyl	**29**	76%
6	**16**	*p*-methoxyphenyl	*m*-methylaniline	**23**	56%	13	**26**	2-furyl	2-furyl	**30**	73%
7	**17**	2-furyl		**24**	26%	14	**26**	2-furyl	cyclopropyl	**31**	79%

(*) Performed in the presence of 1.1 eq. of DBU.

CONCLUSION

We have developed a new and efficient method for the synthesis of [3-(4-aminofurazan-3-yl)-4*H*-[1,2,4]-oxadiazol-5-yl]amine derivatives. We have also enlarged the scope of the 4-aminofurazane chemistry to novel 4-(thiazol-4-yl)furazan-3-ylamine, 4-(pyrimidin-4-yl)furazan-3-ylamine and, 4-(pyrazolidin-3-yl)-furazan-3-ylamine heterocycles.

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10. Analytical and spectroscopic data are shown in the following. **1**: mp 190-192°C (H_2O), (lit.,[5b] 190-191°C); ^{1}H NMR (300 MHz, CD_3OD) δ= 4.90 (br s); ^{13}C NMR (75 MHz, CD_3OD) δ= 155.92, 145.80, 141.19; Anal. Calcd for $C_3H_5N_5O_2$: C, 25.18; H, 3.52; N, 48.94. Found: C, 25.25; H, 3.48; N,

48.91; MS (electrospray): 142 ($M\text{-}H^+$). **4m**: amorphous powder; ^{1}H NMR (300 MHz, DMSO d_6) δ= 9.00 (s, 1H), 6.35 (s, 2H), 3.50 (m, 2x2H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, DMSO d_6) δ= 171.61, 158.89, 155.31, 137.34, 69.94, 57.88, 42.85; MS (electrospray): 225 ($M\text{-}H^+$), 261 ($M+Cl^-$), 451 ($2M\text{-}H^+$). **5**: mp 208-210°C (decomp), (isopropanol); ^{1}H NMR (300 MHz, DMSO d_6) δ= 7.30 (br s, 2H), 6.80 (br s, 1H); ^{13}C NMR (75 MHz, DMSO d_6) δ= 172.46, 159.23, 155.29, 138.99; HRMS (EI): Calcd 169.0236 Found: 169.0233. **9**: mp 136-138°C (CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.50 (br s, 2H), 2.51 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 166.87, 155.10, 154.38, 142.69, 19.28, 13.50. **10**: mp 94-95°C (CH_2Cl_2), (lit.,[7] 96°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.20 (s, 2H), 2.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 192.84, 155.17, 143.49, 28.16; MS (EI) 127 ($M^{+\cdot}$). **11**: mp 162°C (CH_2Cl_2), (lit.,[8b] 162-163°C); ^{1}H NMR (300 MHz, DMSO d_6) δ= 6.50 (br s, 2H), 4.87 (s, 2H); ^{13}C NMR (75 MHz, DMSO d_6) δ= 184.72, 155.67, 141.91, 34.34; MS (EI) 207, 205 (M^+). **13f**: amorphous powder; ^{1}H NMR (300 MHz, CD_3OD) δ= 7.20 (s, 1H), 4.80 (br s, 4H); ^{13}C NMR (75 MHz, CD_3OD) δ= 171.70, 156.40, 142.38, 136.42, 109.07; MS (electrospray): 182 ($M\text{-}H^+$), 228($M+HCOO^-$), 262, 264 ($M+Br^-$); MS (electrospray): 184 ($M+H^+$), 225 ($M+CH_3CN+H^+$). **15**: mp 109°C (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.10 (d, *J* = 15.6 Hz, 1H), 6.80 (dd, *J* = 15.6 and 11.3 Hz, 1H), 5.20 (br s, 1H), 1.75 (m, 1H), 1.15 (m, 2H), 0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 182.11, 158.81, 156.05, 143.32, 123.09, 15.98, 10.25; MS (electrospray): 180 ($M+H^+$). **22**: mp 122-124°C (Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.40-7.20 (m, 6H), 5.55 (br s, 1H), 5.20 (br s, 2H), 4.58 (d, *J* = 6.2 Hz, 2H), 1.95 (m, 1H), 1.15 (m, 2H), 1.05 (m, 2H); MS (electrospray): 309 ($M+H^+$); MS (electrospray): 307 ($M\text{-}H^+$), 343 ($M+Cl^-$), 367 ($M+CH_3COO^-$), 651 ($2M+Cl^-$). **27**: amorphous powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.32 (s, 1H), 6.38 (m, 1H), 6.34 (m, 1H), 5.71 (m, 1H), 5.20 (br s, 2H), 3.15 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.65, 154.27, 150.83, 142.52, 142.43, 140.24, 110.70, 108.53, 53.20, 38.32, 22.01.