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N, N-Dimethylamino acrylate derivatives - Facile inexpensive synthesis of Rufinamide-an antiepileptic & Allopurinol-a drug for gout

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ABSTRACT

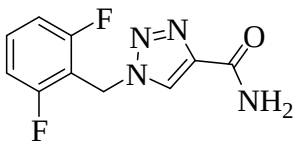
A new protocol for the facile synthesis of Rufinamide and Allopurinol medicaments is developed by the utilization of N, N- dimethylamino acrylate derivatives.

Keywords: N, N- dimethylamino acrylate derivatives, Rufinamide, Allopurinol, Medicaments.

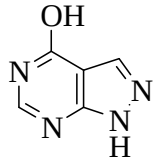
INTRODUCTION

Rufinamide **1**, a triazole derivative is an anticonvulsant medication used in combination with other medication and therapy to treat Lennox-Gastaut Syndrome and various other forms of epilepsy [1]. Among the various antiepileptic drugs (AEDs), Rufinamide is the one recently approved by USFDA for effective controlling of seizures. It is presumed to involve stabilization of the sodium channel inactive state, effectively keeping these ion channels closed.

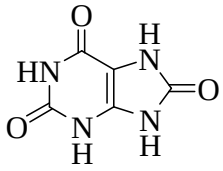
Allopurinol **2** is a structural isomer of hypoxanthine (a naturally occurring purine in the body) and is an enzyme inhibitor of xanthine oxidase [2]. It is used to treat chronic gout ("the king of diseases and the disease of kings" or "rich man's disease") [3]. Gout is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis – a red, tender, hot, swollen joint. It may also present as tophi, kidney stones, or urate nephropathy, which is caused by elevated levels of uric acid **3** in the blood which crystallize and are deposited in joints, tendons and surrounding tissues.



1
Rufinamide



2
Allopurinol



3

MATERIALS AND METHODS

^{1}H & ^{13}C NMR spectra are recorded using a Bruker 400 Spectrometer (400 & 100 MHz respectively) with TMS as internal standard. Mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV. IR spectra are recorded on Perkin Elmer Spectrophotometer as KBr pellets or neat. Analytical TLC is conducted on E-Merck 60F254 aluminum-packed silica gel plates (0.2mm). Developed plates are visualized using UV light or Iodine chamber. HPLC spectra are recorded on shimadzu 2010.

General Procedure for the synthesis of Rufinamide [1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide] (1)

A mixture of 2,6-difluorobenzyl azide **4** (20.0gm, 0.118 M) and methyl-2-(dimethylamino)ethyl acrylate **5** (38.1gm, 0.29 M) were heated to 130 - 135°C and stirred for 4 hrs. (The completion of the reaction was monitored by TLC). After completion of the starting material, reaction mass was cooled to RT and added 20% methanolic ammonia solution (200.0 mL). Stirred for 24 hrs at ambient temperature, then heated to reflux temperature (65 – 70°C) and stirred for 2 hrs. The reaction mass was gradually cooled to 5- 10°C. DM Water (30.0 mL) was added and stirred for 30 min and collected the solids through filtration and washed the cake with chilled methanol (20.0 mL). White crystalline solid is obtained. Yield: 74 %; mp: 238–239 °C (lit [4]: 236-238°C); DSC: 241.59°C; HPLC purity: 99.98 %; FT-IR (cm^{-1}): 3412 ($-NH_2$), 3093, 2317, 1634 (C=O), 1473, 1398, 1235, 1037, 798; ^{1}HNMR (ppm, DMSO): δ 8.56 (s, 1H), δ 7.88 (s, 1H), δ 7.55 (m, 2H), δ 7.15 (t, 2H, *J* = 8.0 Hz), δ 5.72 (s, 2H); ^{13}CNMR (DMSO/TMS): δ 162.42, 161.68, 159.94, 143.18, 132.17, 127.18, 112.43, 112.19, 111.40, 41.54; ^{19}FNMR (ppm, DMSO): δ 114.51 (s, 2F); ESI-MS (m/z %): 239.3 (M+1, 100%), 127.2 (80%), 261.2 (60%).

Data for ester **6**: mp: 133–135 °C; HPLC purity: 99.0 %; FT-IR (cm^{-1}): 3132, 1722 (C=O), 1628, 1594, 1545, 1469, 1347, 1232, 1048, 1027; ^{1}HNMR (ppm, DMSO): δ 8.10 (s, 1H), δ 7.42 – 7.38 (m, 1H), δ 6.99 (t, 2H, *J* = 8.0), δ 5.68 (s, 2H), δ 3.92 (s, 3H); ^{13}CNMR (DMSO/TMS): δ 162.47, 160.94, 159.91, 140.09, 131.80, 127.41, 111.98, 111.74, 109.94, 52.10, 41.62; ^{19}FNMR (ppm, DMSO): δ 113.95 (s, 2F).

General Procedure for the synthesis of Allopurinol (2)

a) Synthesis of 3-Amino-4-carbethoxy pyrazole sulfate salt **(8)**

Ethyl-2-cyano-3-(dimethylamino)acrylate **7** (102.0gm, 0.606 M) was dissolved in methanol (408.0 mL) at room temperature and added hydrazine hydrate [(38.0gm, 1.25 M) 45.0 mL of 85% aqueous solution] drop wise at RT under nitrogen atmosphere. Stirred for 10 hrs at RT (The completion of the reaction was monitored by TLC). Evaporated methanol completely under vacuum at 45°C and added ethyl acetate (955.0 mL) at 20-25°C and stirred for 10 min to get clear solution. Washed with water (100.0mL X 2) and sat. brine solution (100.0mL) and then distilled out half of the solvent and given carbon treatment (10.0gm) to the remaining solution. Added conc. Sulfuric acid (59.0gm 1.0 M) drop wise with external cooling (0 – 5°C). Stirred for 1 hr and collected the solids through filtration and washed with ethyl acetate (50.0mL X 2). Off-White powder; Yield: 84 %; HPLC purity: >99 %; mp: 176 - 180 °C; FT-IR **(**cm^{-1}**)**: 3431 (-NH_2), 3312 (-NH), 1715 (C=O), 1639, 1566, 1335, 1211, 1123, 1079, 887, 597; ^{1}HNMR (ppm, DMSO): δ 11.78 (broad, s, 1H, -NH), δ 7.39 (s, 1H, -CH), δ 5.94 (s, 2H, -NH_2), δ 4.13 (q, 2H, *J* = 6.9 Hz, -CH_2), δ 1.22 (t, 3H, -CH_3); ^{13}CNMR (DMSO/TMS) δ, 164.01, 156.57, 151.58, 139.77, 131.82, 93.78, 58.83, 14.82.

b) Synthesis of 1H-pyrazolo[3,4-d] pyrimidin-4-nol **(2)**

3-Amino-4-carbethoxy pyrazole sulfate salt 8 (126.0gm, 0.497M) and 504.0 mL formamide were heated to 165 – 170^{o}C under N_2 atmosphere and stirred for 14 to 16 hrs (Completion of the reaction was monitored by TLC). After completion of the starting material, cooled the slurry to RT and further to 0 – 5^{o}C. Stirred for 1 hr and filtered the material. The obtained material (60.0gm) was dissolved in 5% aqueous NaOH solution (540.0 mL) at RT and treated with activated carbon (6.0gm). The aqueous layer pH adjusted to 3.5 to 4.0 with 2N HCl solution (370.0 mL) and stirred for 30 min at RT. Collected the solids through filtration and washed with DM Water (100.0mL X 3) and finally with acetone (50.0mL X 3). Off-White powder; Yield: 81 %; FT-IR (cm^{-1}): 3166 (NH), 3081, 3043, 2992, 2938, 2877, 1975, 1699 (C=O), 1586, 1478, 1389, 1366, 1239, 1228, 1159, 1085, 955, 913, 884, 813, 781, 707, 604 and 540; ^{1}HNMR (ppm, DMSO): δ 12.7 – 12.4 (broad, s, 2H, -NH & -OH), δ 8.1 (s, 1H, -CH), δ 7.9 (s, 1H, -CH); ^{13}CNMR (DMSO/TMS) δ, 158.16, 155.0, 147.88, 134, 105.89; ESI-MS (m/z %): 137.1 (M+1, 100%).

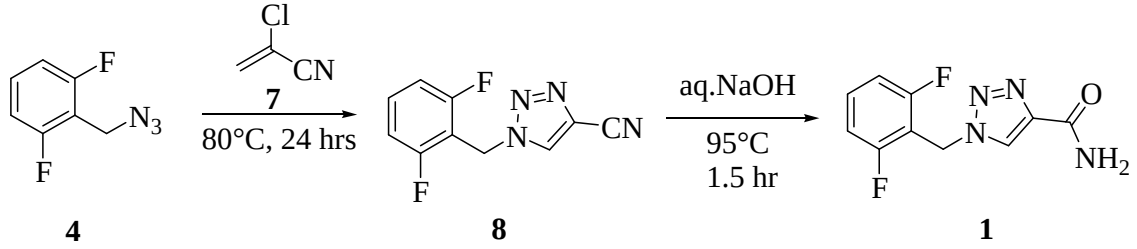
RESULTS AND DISCUSSION

In continuation of our earlier work [5], now we wish to report our studies on the application of N, N-dimethylamino acrylate derivatives in the optimized preparation of Rufinamide and Allopurinol medicaments. The construction of heterocycles is an important aspect in synthetic organic chemistry. The process should be simple and should not contain tedious work-up for scale-up in industry as well as academics. As already mentioned the dimethylamino acrylate derivatives can be easily prepared from abundantly available inexpensive raw-materials i.e. DMF and DMS. These acrylate derivatives can be effectively used for the construction of many heterocycles bearing triazoles, pyrazoles, pyrazolo pyrimidines, oxazoles, isoxazoles, thiazoles etc. which are the building blocks for many biologically active molecules.

Rufinamide is an anti epileptic drug possessing triazole ring. Several synthetic routes have been reported earlier [4, 6, 7, and 8]. All the routes were mainly concentrated on the construction of triazole ring only by the cycloaddition of dipolarophile with the azide starting material, prepared

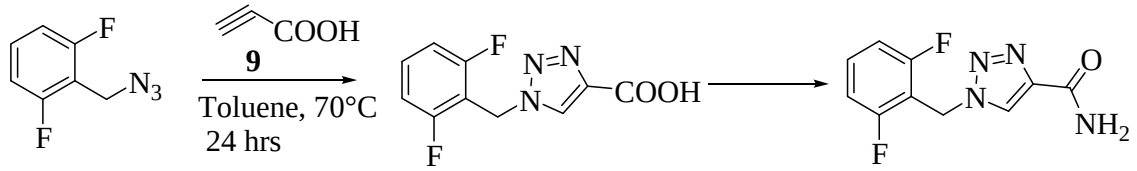
according to known procedures. The four different dipolarophiles reported are ethyl propiolate [4], propiolic acid [6, 7], 2-chloroacrylonitrile [7, 8] and methyl-3-methoxyacrylate [9]. All the dipolarophiles are expensive compared to methyl-2-(dimethylamino) ethyl acrylate prepared according to our previous procedure and 2-chloroacrylonitrile is highly toxic and flammable.

To overcome the shortcomings of the reported syntheses **(Scheme 1, 2 & 3)**, we sought to adopt our previously reported "N, N-dimethylamino methoxy methylenium methyl sulfate" adduct methodology for the optimized preparation of Rufinamide and Allopurinol. Following this methodology we were successful in developing facile and inexpensive method that generates less waste than the established methods.



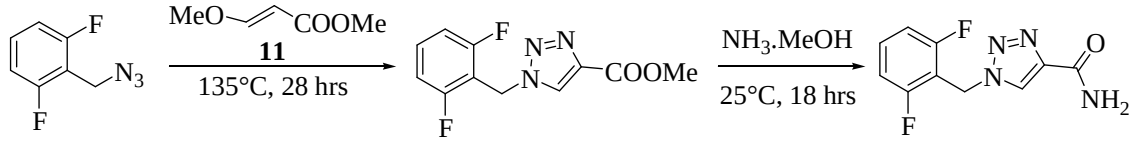
4 **8** **1**

Scheme 1: Synthesis of Rufinamide from nitrile 7



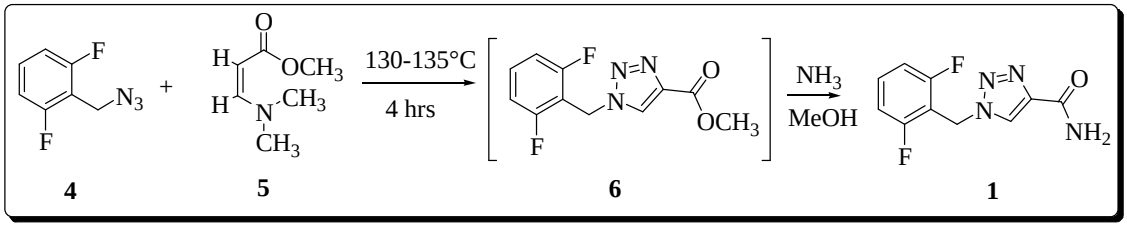
4 **10** **1**

Scheme 2: Synthesis of Rufinamide from propiolic acid 9



4 **6** **1**

Scheme 3: Synthesis of Rufinamide from enol ether 11



4 **5** **6** **1**

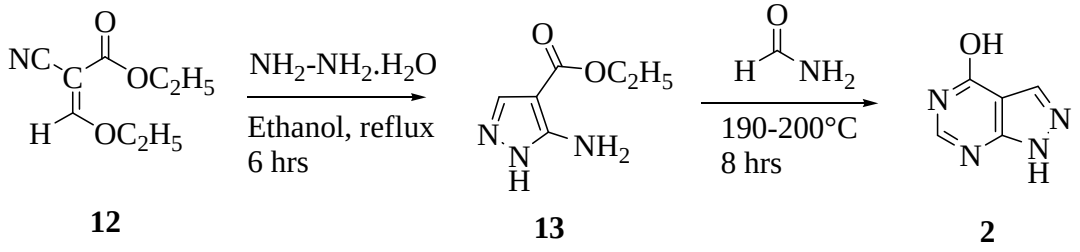
Scheme 4: Synthesis of Rufinamide from 5.

Our synthesis of Rufinamide begins with the cycloaddition of azide **4** with methyl-2-(dimethylamino) ethyl acrylate **5 (Scheme 4)** without solvent followed by treatment with methanolic ammonia in one pot synthesis. The cycloaddition is performed at 130 to 135°C for 4 hours and upon completion, cooling to RT ammonolysis of the ester intermediate is carried out smoothly in methanolic ammonia yielding **1** in 74% overall yield. Initially the cyclisation is

carried out with 1:1 mole ratio of azide **4** and acrylate **5** followed by ammonolysis. But here the yield obtained is only 48%. So, to improve the yield slight excess of acrylate (2.5:1) is taken for the cycloaddition reaction.

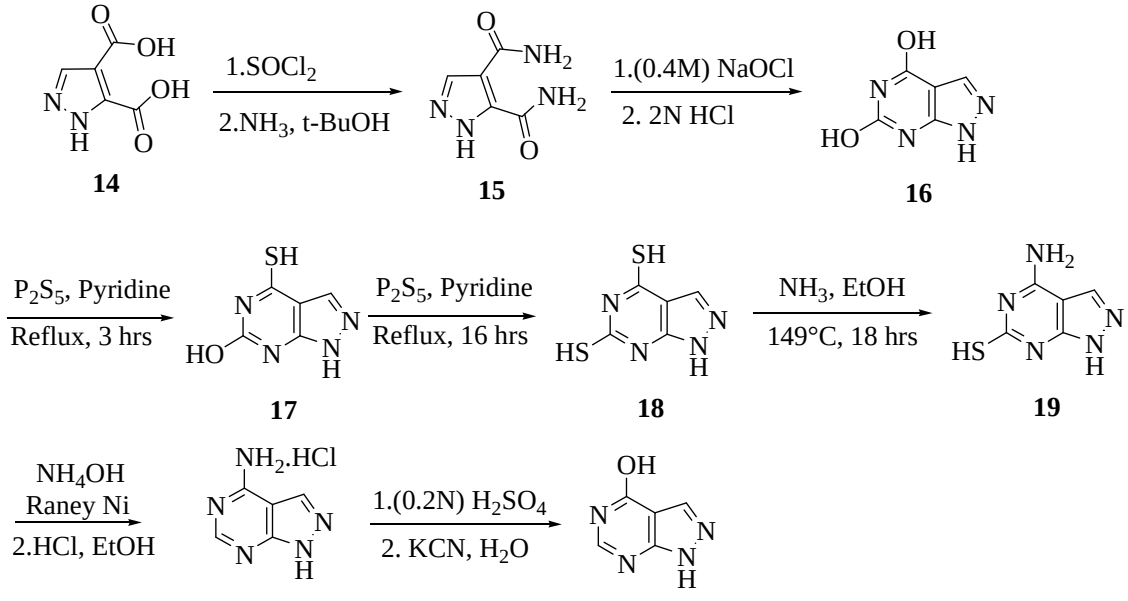
Dimethylamino acrylate derivatives have the same oxidation state as alkynes and can serve as alkyne synthons. Cycloaddition of these acrylates with alkyl azide results in 1,2,3-triazoline intermediate and with hydrazine hydrate results in pyrazoline intermediate which lose dimethylamine to aromatize the ring. The regiochemistry of the cycloadditions is controlled by the leaving group i.e. dimethylamine which is lost during the reaction [10].

Earlier syntheses of Allopurinol reported from ethoxy-methylene-cyanoacetic acid ethyl ester **12** [11] **(Scheme 5)**, pyrazole-3,4-dicarboxylic acid **14** [12] **(Scheme 6)**, cyanoace- -tamide **21** [13] **(Scheme 7)**, 4,6-dichloro-5-formylpyrimidine **25** [14] **(Scheme 8)**.



12 **13** **2**

Scheme 5: Synthesis of Allopurinol from 12.

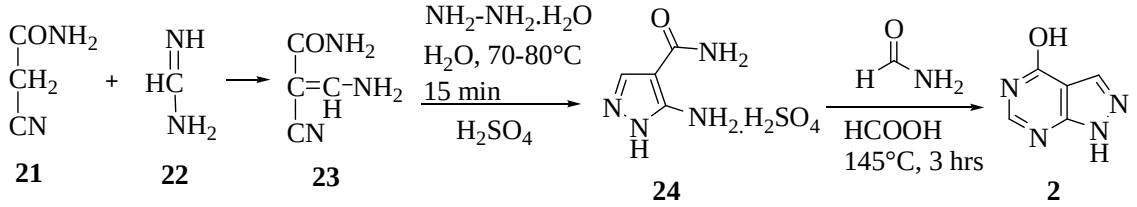


14 **15** **16** **17** **18** **19** **20** **2**

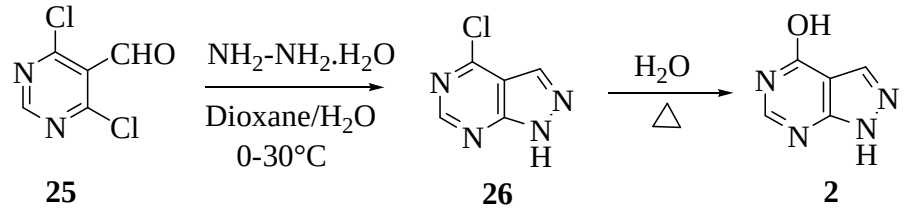
Scheme 6: Synthesis of Allopurinol from 14.

We have synthesized **2,** starting from ethyl-2-cyano-3-(dimethylamino) acrylate **7** in two step processes. First treating **7** with 85% hydrazine hydrate in methanol as solvent medium at room temperature followed by sulfate salt preparation of the formed amino pyrazole ring. Then further cyclisation is carried out with formamide at 165-170°C afforded light gray color solid which on

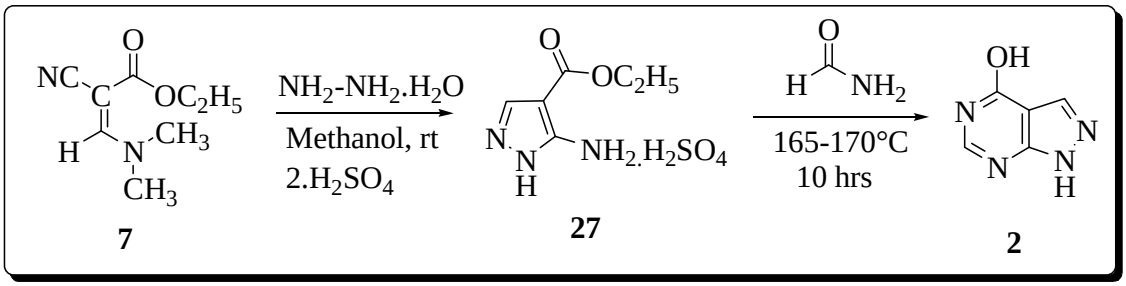
purification from dilute alkali solution and activated charcoal treatment resulted in off-white to white solid.



Scheme 7: Synthesis of Allopurinol from 21



Scheme 8: Synthesis of Allopurinol from 25.



Scheme 8: Synthesis of Allopurinol from 7.

CONCLUSION

In conclusion, we have demonstrated a new protocol for the facile and inexpensive synthesis of Rufinamide and Allopurinol drugs bearing heterocycles by the utilization of N, N-dimethylamino acrylate derivatives.

Acknowledgments
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