A fast heterocyclic three component synthesis of imidazo[1,2-a] annulated pyridines, pyrazines, pyrimidines and thiazoles under microwave conditions

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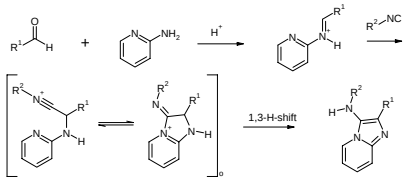
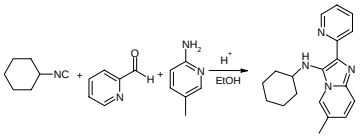
Introduction: Multicomponent reactions are becoming more popular nowadays since they provide a possibility to introduce a large set of diversity to different substance classes in one step. The imidazo[1,2-a]pyrazine, -pyridine, -pyrimidine and -thiazole structural moieties can be found in pharmacologically active compounds, such as anti-inflammatory agents, (Miroprofen)[1], calcium channel blockers[2] and antibacterials[3]. In 1998, three different research groups discovered a novel reaction at almost the same time[4]. They found (partly by serendipity) that when using 2-aminopyridines as the amine component together with isonitriles and aldehydes in the Ugi 4 component reaction (4CR) the formation of imidazo-pyridines was observed. The acid, the fourth component of the Ugi 4CR, is required as a catalyst. Under conventional conditions, the reaction takes 18-72 h depending on the method used to give the products in high yield.

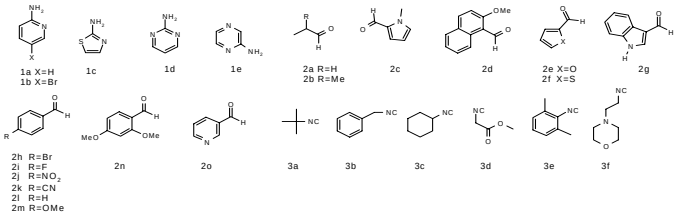


In 1999 Varma *et al.* published this reaction under microwave and solvent-free conditions in a two-step fashion[5]. The two-step procedure introduces a limitation since alkyl iminium ions can be unstable and the solvent free procedure is inconvenient when it comes to library production. Especially when automated liquid handlers are used, but also due to the fact that many products are highly crystalline, making the isolation problematic.

We therefore followed the papers developed by Groebke *et al.* and Bienaymé *et al*. in order to find a solution phase protocol under microwave conditions and with short reaction times[6]. First we tried the method by Groebke *et al.* who used 2 eq. of acetic acid as catalyst. After up to 30 min at 170 °C in EtOH we only found traces of product (LC/MS analysis). Bienaymé used perchloric acid as the protic acid needed for the reaction. Perchloric acid may cause an explosion when heated and is therefore considered not to be very suitable for microwave heating. But in a closed pressurized vial and in only catalytic amounts we did not find any problems.
170 °C for 5 min was found to be a fairly general protocol.



The table below shows some structural variations tolerated by these reaction conditions. Both aromatic, aliphatic (even sterically hindered) and heteroaromatic aldehydes were used and gave the corresponding products in acceptable to good yields. The same is true for the isonitriles and heteroaromatic amidines used. It should be noted, though, that the yields presented in the table are based on the product peak area as compared to total peak area of the LC chromatogram (LC purity). As described above some of the products are highly crystalline, and in those cases were the products precipitated directly from the reaction mixture, the products were isolated by a simple filtration. No further purification was needed. (No recovery from the mother liquor implies that the total yield could be higher). When scaling up the synthesis [18 times], substrates 1b, 2j & 3e gave the isolated product in 70 % yield, as in the original protocol, see table below.



Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]	Compound	Yield[a]
1a2b3a	83	1a2k3c	97	1b2g3a	50	1b2m3a	83	1e2a3d	63 (42)
1a2f3a	60	1a2l3a	82	1b2i3a	76 (71)	1b2j3c	-- (70)	1e2a3f	62 (17)
1a2f3b	57	1a2l3c	97	1b2i3c	23 (58)	1b2n3a	95	1e2d3d	64 (44)
1a2g3a	69	1a2m3a	78	1b2i3e	38	1b2n3c	98	1e2d3f	57 (9)
1a2g3c	69 (37)	1a2m3b	74	1b2j3a	28 (54)	1c2a3d	39	1e2e3f	49
1a2i3a	75	1a2n3c	95	1b2j3e	-- (71)	1c2d3d	42 (21)	1e2h3d	39
1a2i3c	93	1b2b3a	75	1b2k3a	57 (51)	1c2d3f	35	1e2h3f	81 (9)
1a2j3a	82	1b2c3e	76	1b2k3c	16 (66)	1d2c3a	62	1e2o3d	46
1a2j3b	29 (62)	1b2c3a	62	1b2k3e	11 (76)	1d2d3d	42	1e2o3f	55
1a2j3c	27 (66)	1b2g3e	59 (53)	1b2l3a	89 (32)	1d2e3d	36		
1a2k3a	83	1b2f3a	75 (46)	1b2l3c	56 (58)	1d2h3d	20 (9)		
1a2k3b	76 (54)	1b2f3c	8 (60)	1b2l3e	56	1d2o3d	39		

[a]= LC purity, in parentheses: isolated yield after filtration of the precipitated product.

References

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