Synthesis and Reactions of Aroyl Substituted Enone Mannich Salts [1])

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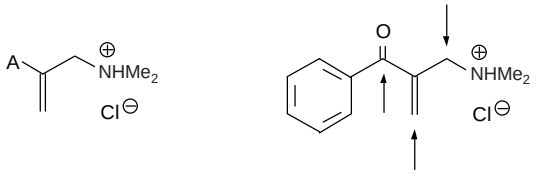
Abstract. The classical Mannich reaction of aromatic methyl ketones with paraformaldehyde and dimethylamine hydrochloride resp. dimethyl(methylene)ammonium chloride has been extended to a few cases of 1-aryl-2-dimethylaminomethyl-prop-2-en-1-ones (ADMP reagents). They have gained remarkable attention in medicinal chemistry, but only more recently their properties as valuable building blocks for ring closure reactions to form either aroyl or dimethylaminomethyl substituted heterocyclic compounds has been evaluated. In this review, a collection of representative examples for their preparation (Scheme 2) and biological effects as well as the synthetic potential for the synthesis of heterocycles (Scheme 3–8) is given. The reaction of 4-hydroxycoumarin delivers with ADMP reagents, *via* the formation of detectable 3-(2-benzoylallyl)-4-hydroxycoumarins as secondary substitution products, after ring closure 3-benzoyl-3,4-dihydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]pyran-5-ones (Scheme 4). The reaction of 4-hydroxy-6-methylpyran-2-one with ADMP reagents is investigated systematically in order to assess its suitability in carbon–carbon bond forming reactions as well as to provide the conditions for subsequent ring closure or intermolecular addition of further nucleophiles to the enone double bond of the intermediate 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones yielding miscellaneous 3-substituted 2-pyrones (Scheme 5 and 8), and their application as building blocks for the combinatorial chemistry. The condensation of ADMP reagents with 2-aminopyridines gives rise to 3-benzoyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines (Scheme 6) and the corresponding reaction using amidines affords 5-benzoyl-1,4,5,6-tetrahydropyrimidines (Scheme 7).

1-Aryl-2-dimethylaminomethyl-prop-2-en-1-ones (ADMP reagents) belong to the powerful class of *N*,*N*-dimethylallylammonium salts with electron-acceptor substituent in position 2, *i.e.* CN [1], COR (R = aliphatic substituent) [2], COOR [3], COOH [4]. They are characterized by three different electrophilic reaction centers which can be attacked by ambifunctional nucleophilic reagents to form either aroyl- or dimethylaminomethyl substituted heterocyclic compounds (Scheme 1). The aim of this short report is to collect some representative examples of ADMP reagents for describing the preparation, the significance in medicinal chemistry and above all to demonstrate their usefulness in modern synthetic heterocyclic chemistry.



A = CN, COR, COOR, COOH ADMP reagent

Scheme 1 *N*,*N*-Dimethylprop-2-enylammonium salts with electron-acceptor substituent in position 2

In the course of our attempts to synthesize 4-aryl-1,8-naphthyridines *via* cyclization of 2-(3-hydroxy-3-phenylpropylamino)pyridines we failed to aminomethylate 3,4-dichloroacetophenone under standard conditions; a comprehensive review on modern variants of the Mannich reaction has been recently published [5]. Dimmock *et al.* obtained the Mannich base of this ketone in a yield of only 30% using 1,2-dimethoxyethane as solvent [6]. Thus, we considered enforcing this reaction by employing dipolar aprotic solvents which are occasionally used in Mannich reactions [7]. When carrying out the reaction in dimethylformamide the normal Mannich product **3** was formed only in traces and the aminomethylated propenone derivatives **2** were isolated in moderate yields [8]. This solvent has the major advantage that the reaction will be suitable for acid labile aryl methyl ketones [9] as well and the procedure is much easier to perform than alternative synthesis. When employing preformed iminium salts, the so-called Böhme salts [10], an improvement of the yield is noticeable. A reasonable reaction mechanism involves attack of the methyl ketone by two molecules of the Mannich reagent to give **4** followed by elimination of dimethylamine producing the propenone derivative **2** (Scheme 2). These experimental results prompted us to investigate the general applicability of dimethylformamide as

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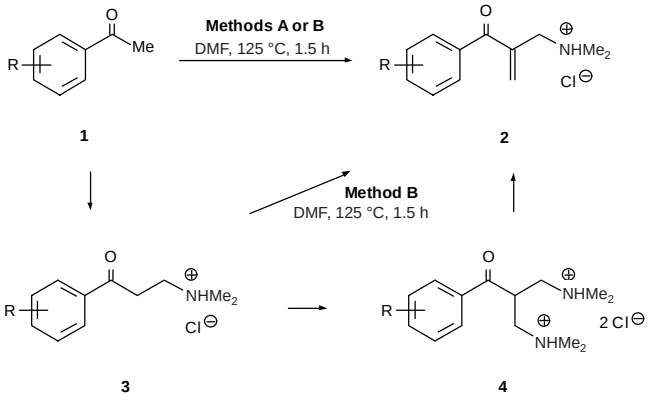
a solvent for the Mannich reaction of aromatic methyl ketones.



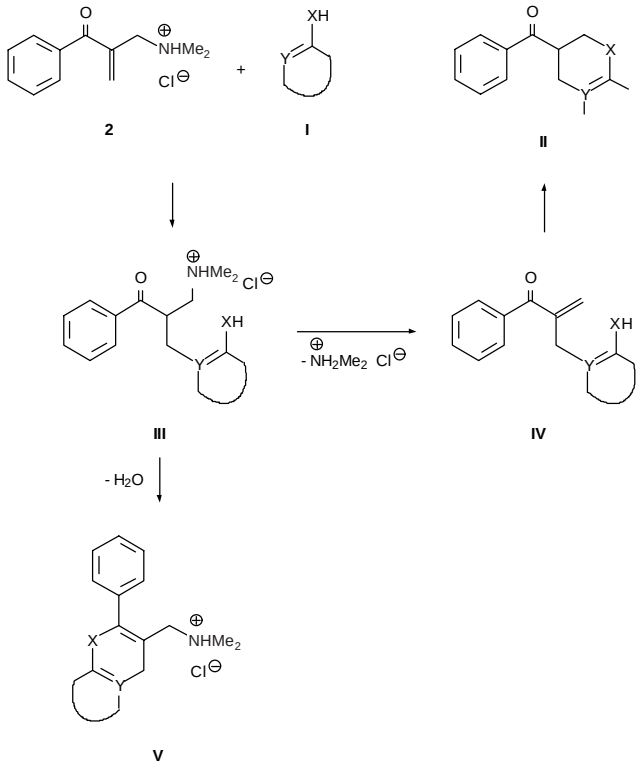
R = H, Br, Cl, Me, OMe
Method A: $(CH_2O)_n$ (3 equiv.), Me_2NH_2Cl (2 equiv.), 24 – 44%
Method B: $CH_2{=}NMe_2Cl$, 38 – 66%

Scheme 2 Synthesis of enone Mannich salts (ADMP reagents) **2**

Despite the extensive use of 1-aryl-2-dimethylaminomethylprop-2-en-1-ones **2** for *in vitro* and *in vivo* studies, the synthesis of these structures is hampered by either low yields or the formation of mixtures consisting of the normal Mannich product **3** and the propenone **2**. Thus, there are only a few cases that more than one aminomethyl group is introduced into the same substrate [11–13], thus producing a methylene-bis-derivative, which in turn may undergo deamination [11, 12, 14–16] with formation of an aminomethylated prop-2-en-1-one derivative. Some of them were synthesized by treating the hydrochlorides of the corresponding bis-Mannich bases **4** with Sorensen phosphate buffer, pH 7.4, in a purity of ca. 95% proved by HPLC [6]. And indeed, the bis-Mannich products **4** can and have been investigated as prodrugs for the propenones **2** [17]; a simple procedure for the synthesis of bis-Mannich bases has been recently published [18]. For the synthesis of the propenone **2** the aryl methyl ketone **1** is brought to reaction with paraformaldehyde and the appropriate amine, the use of glacial acetic acid [19–26] or even 3-methylbutanol in the presence of concentrated hydrochloric acid [27] as solvents have been reported.

1-Aryl-2-dimethylaminomethylprop-2-en-1-ones with the general structure **2** have gained remarkable attention in medicinal chemistry as antimicrotubular agents [19, 28], anticonvulsants [29], they show antileukemic activity [6, 17, 30], and the inhibition of the epidermal growth factor (EGF) tyrosin kinase by benzyloxy substituted **2** has been shown only recently [20]. Even their antifungal activity [19, 31] has been reported.

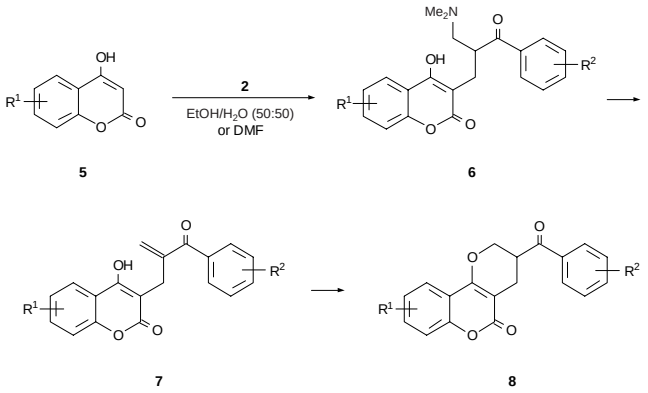
According to the structure of the ADMP reagents the conclusion may be drawn that altogether three electrophilic centers (Scheme 1) can be involved in an addition-elimination mechanism which enables these versatile reagents to be excellent precursors for ring closure reactions using bifunctional nucleophiles. Surprisingly, a study of the literature revealed that such an application has not yet found its way into modern synthetic heterocyclic chemistry. Up to now, only a few reactions with ADMP reagents have been reported [32–35] demonstrating their valuable C–C, C–O, C–S, and C–N bond forming potential. The polyfunctional character of both educts is the reason why the result of a ring closure reaction cannot be predicted. Scheme 3 shows a possible reaction mechanism using a heterocyclic dinucleophilic reagent. Generally, the ring closure is initiated by nucleophilic attack at the enone double bond affording the β-aminoketone **III**. Next, the third electrophilic center is generated by amine elimination to form the enone **IV** followed by a second addition reaction to the ring closed heterocycles **II** or **VI**. Another mode of action is the attack at the keto carbonyl group of **III** to give 3-aminomethylated pyranes **V** and/or conceivable tautomeric follow-up products in analogy to **VI**.



Scheme 3 Possible mechanism for the reaction of **2** with dinucleophilic reagents

In order to study the influence of the polyfunctional electrophilic as well as nucleophilic character of the re-

actants, condensations of enone Mannich salts **2** with representative *O*,*C*-, *N*,*N*-, *C*,*N*-, and *S*,*N*-nucleophiles were performed. In accordance with the addition-elimination mechanism mentioned above, we found a procedure for preparing 3-benzoyl-3,4-dihydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]pyran-5-ones **8** [32] in up to 84% yield by heating 4-hydroxycoumarin **5** with two equivalents of ADMP reagent **2** in dimethylformamide as solvent to 130–140 °C for 1.5 hours (Scheme 4). Where-

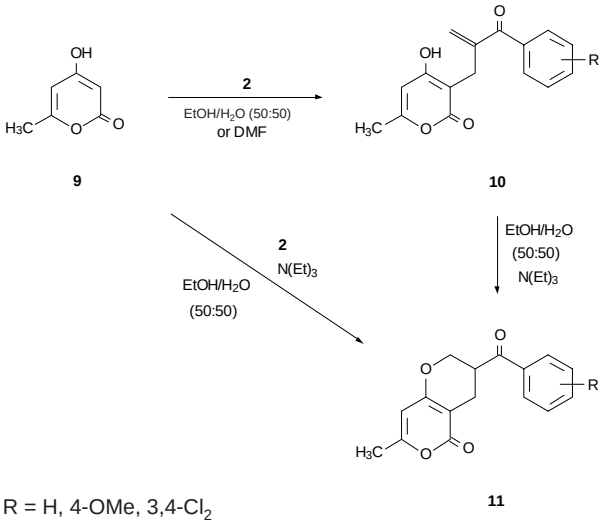


$R^1 = R^2$ = H, Me, OMe, Cl, Br

Scheme 4 Synthesis of 3-benzoyl-3,4-dihydro-2*H*,5*H*-1-benzopyrano[4,3-*b*]pyran-5-ones **8**

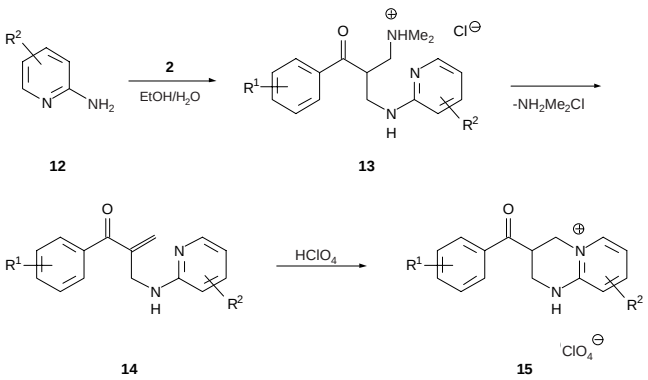
as **6** could not be isolated, the intermediate enone **7** was detected by tlc and could be characterized when heating was stopped already after 15 minutes as a mixture together with **8**. Compounds analogous to **V** and **VI** shown in Scheme 3 could not be detected. Contrary to the corresponding reaction of 4-hydroxycoumarin **5** heating the 4-hydroxy-6-methylpyran-2-one (**9**) with two equivalents of the hydrochlorides **2** in dimethylformamide as the solvent to 120–130 °C for 1 hour gives rise to 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones (**10**) in up to 65% yield [33]. A second addition to form the ring closed heterocycle **11** does not take place. But another approach proved successful in the exclusive formation of the pyranopyrane **11** in yields of 50 to 70%, namely reacting a solution of the educts in 2-propanol in the presence of triethylamine (Scheme 5).

2-Aminopyridines **12** as *N*,*N*-bifunctional nucleophilic reagents are condensed with ADMP reagents **2** to give 3-substituted pyrido[1,2-*a*]pyrimidines **15** (Scheme 6) isolated as perchlorates via the intermediates **13** and **14** which were not found [34]. The more reactive nucleophilic centers of amidines **16** were cyclized with enone Mannich salts **2** to form 5-benzoyl-1,4,5,6-tetrahydropyrimidines **17** (Scheme 7) without detecting any intermediates structurally related to **III**–**V** shown in Scheme 3 [35].



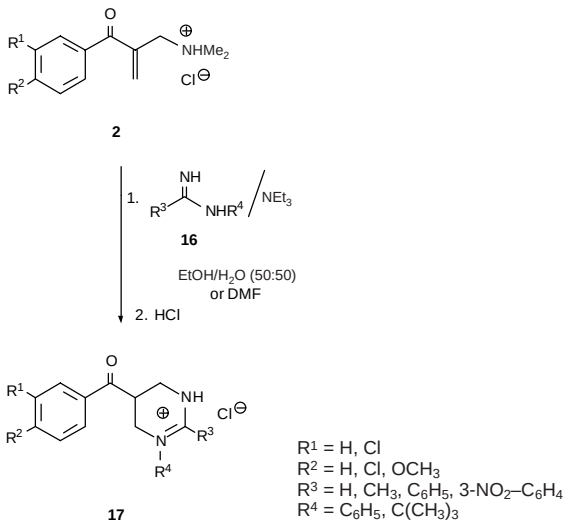
R = H, 4-OMe, 3,4-Cl_2

Scheme 5 Reactions of 4-hydroxy-6-methylpyran-2-one (**9**) with ADMP reagents **2**



R^1 = H, Me, OMe, Cl, Br; R_2 = H, Me

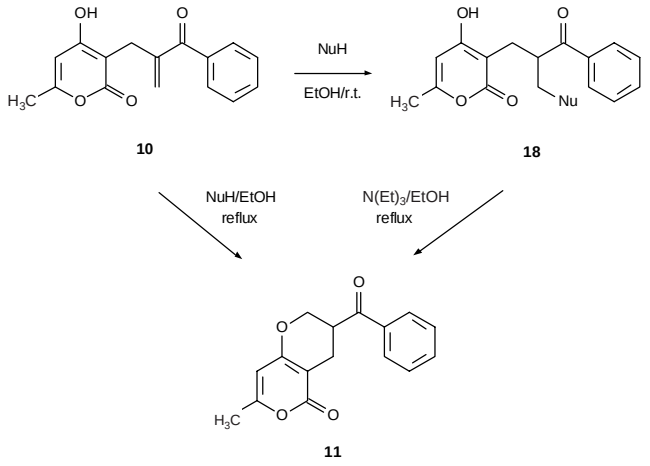
Scheme 6 Synthesis of 3-benzoyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidines **15**



R^1 = H, Cl
R^2 = H, Cl, OCH_3
R^3 = H, CH_3, C_6H_5, 3-NO_2–C_6H_4
R^4 = C_6H_5, $C(CH_3)_3$

Scheme 7 Synthesis of 5-benzoyl-1,4,5,6-tetrahydropyrimidines **17**

The unexpected formation of the ring opened 2-pyranone **10** prompted us to investigate some nucleophilic addition reactions to their enone structure [36]. In first attempts we added amino compounds as examples for *N*-nucleophiles and obtained the *β*-aminoketones **18**. The corresponding *β*-ethoxyketone *β*-benzylmercaptoketone were obtained when using sodium ethoxide as *O*-nucleophile and benzylthio alcohol as *S*-nucleophile [33]. It is noteworthy to mention that the nucleophilic addition has to be performed at ambient temperature. Otherwise, follow-up reactions take place, mainly elimination of the nucleophile and ring closure to form **11** (Scheme 8).

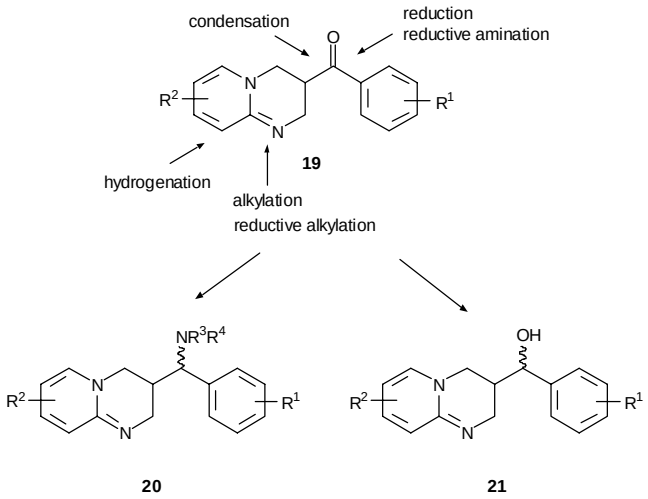


NuH = $PhCH_2NH_2$, *n*-$BuNH_2$, $(Me)_2NH$, $HO(CH_2)_2NH_2$, Pyridin-2-NH_2, EtOH, $PhCH_2SH$

Scheme 8 Nucleophilic substitution reactions of 3-(2-benzoylallyl)-4-hydroxy-6-methylpyran-2-ones (**10**)

The general reaction pathways in nucleophilic additions described above prompted us to investigate the suitability of the enones **10** as building blocks for combinatorial chemistry. Thus, three benzoylallyl derivatives **10** were brought to reaction with a mixture of five amines, namely diethylamine, morpholine, *i*-propylamine, *n*-butylamine, and benzylamine producing a small library in solution. The reaction afforded a mixture of 15 racemates, as one stereogenic center is generated. This mixture was analyzed using liquid chromatography-mass spectrometric coupling. All the expected adducts were found in a comparable amount. This library in solution is stable for a couple of weeks when stored at room temperature [33].

In conclusion, the ADMP reagents **2** are versatile bis-electrophilic reagents. The few examples presented in this short overview demonstrate their synthetic potential for ring closure reactions using bifunctional nucleophiles. Besides the formation of 6-ring heterocycles the preparation of selected 5- and 7-membered are at present under study. The resulting heterocyclic compounds are



Scheme 9 Functionalization of the pyrido[1,2-*a*]pyrimidines **19** as a tool for the synthesis of potential drug molecules

not only interesting targets themselves but are also valuable educts for reduction or condensation processes giving potential drug molecules, *e.g.* the compounds **20** and **21** from the pyridopyrimidines **19** (Scheme 9). In many cases, they are characterized by the classical pharmacophoric structure consisting of aromatic nucleus and side chain with a basic center being incorporated in to a ring system [37]. Furthermore, successive addition of different nucleophiles to ADMP reagents **2** has made them to powerful building blocks with a tremendous synthetic potential in combinatorial chemistry.

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