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Ethoxymethylenemalonates and Malononitriles (EMM Reagents) as Formic Acid Equivalents: Synthesis of Fused-Imidazoles Under Neutral or Mildly Acidic Conditions

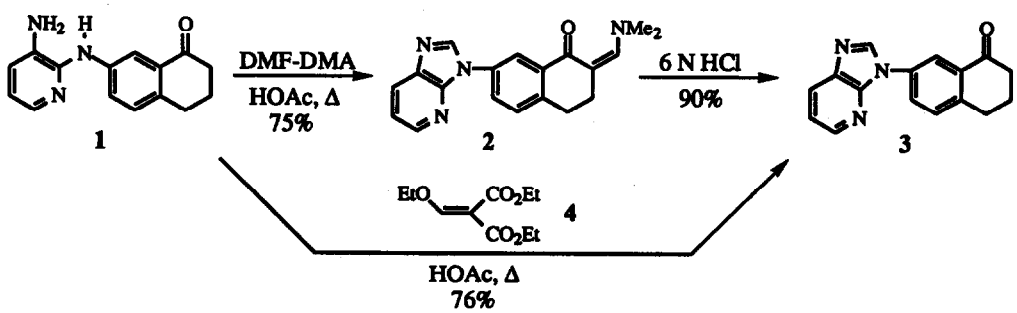
Barb E. Segelstein, Bert L. Chenard,* John E. Macor, Ronald J. Post

Central Research Division, Pfizer Inc., Groton, Connecticut 06340

Key Words: EMM reagents; cyclization; fused imidazoles; imidazolo [4,5-b] pyridines; benzimidazoles

Abstract: *The use of ethoxymethylenemalonates and malononitriles (EMM reagents) for the efficient synthesis of fused imidazoles and related compounds is described.*

Conventional reagents for the closure of ortho diamines to fused imidazoles (anhydrides, orthoformates, dimethylformamide dimethyl acetal) generally require the forcing conditions of strong acid and high temperature for successful reaction.[1,2] Under these conditions, side reactions may also occur, especially with substrates which have additional reactive sites. This was our predicament when we attempted to prepare the imidazolo [4,5-b] pyridine **3** from **1** and dimethylformamide dimethyl acetal in refluxing acetic acid. Although the ring closure was efficient, further reaction occurred adjacent to the tetralone carbonyl to produce **2** in 75% yield. While **2** could be converted to the desired product **3** by refluxing with 6 N HCl, we desired a more direct and general synthesis of the fused imidazoles, preferrably under neutral conditions. We present here, the use of ethoxymethylenemalonates and malononitriles (EMM reagents) for the synthesis of fused imidazoles and thiazoles in what appears to be a general method. The reaction takes advantage of the ability of these reagents to act as double Michael acceptors and the facile elimination of malonate or malononitrile anions to introduce the unsaturation and complete the synthesis. The significance of this simple transformation is magnified by the recent emergence of imidazolo [4,5-b] pyridines as potent inhibitors of angiotensin II, an enzyme which may be important in the regulation of blood pressure.[3]

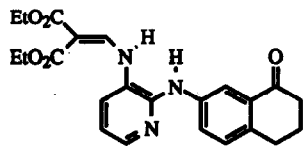


EMM reagents have been used extensively in the synthesis of various six-membered ring species.[4] In general, these ring forming processes involve Michael addition, elimination of ethoxide, and subsequent ring closure

through a cyclization process with one of the ester or nitrile groups. One exception is the reaction of ortho aminobenzamide with EMM reagents.[5] In this case, reaction takes place through two sequential Michael additions to the EMM reagent with subsequent loss of malonate or malononitrile. The key difference between these processes is that the double Michael process seems to be preferred only when the standard process (i.e. Michael addition followed by cyclization on the ester or nitrile) must yield a ring of more than six atoms. Thus, reaction of EMM reagents with 1,2-diamines should yield five membered rings preferentially.[6]

In our initial studies, **1** was treated with diethyl ethoxymethylenemalonate (**4**, 1.2 equiv.) in acetic acid at 100°C and **3** was obtained directly in 78% yield with no evidence of side products from reaction adjacent to the tetralone carbonyl. Only a minor amount of the non-cyclized intermediate **5** and diethyl malonate were found in the crude reaction mixture.

Having established that **4** could effectively deliver a single carbon at the formic acid oxidation level to an 1,2-diamine, we next explored solvent effects to try to escape from acidic reaction media. In refluxing aprotic solvents such as dioxane and chloroform, only intermediate **5** was formed. However, in protic solvents such as ethanol or isopropanol, the desired product **3** was formed efficiently (entries 2, 3, Table 1).



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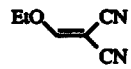

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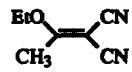

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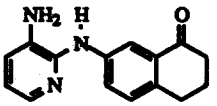
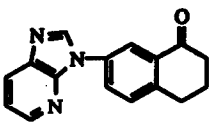
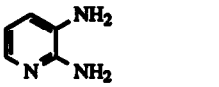
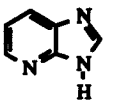
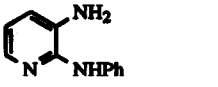
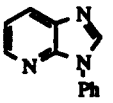
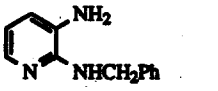
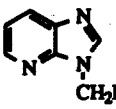
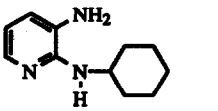
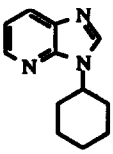
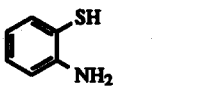
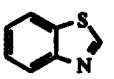
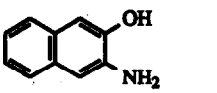
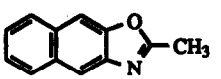
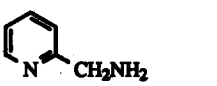
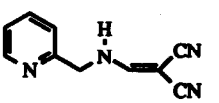
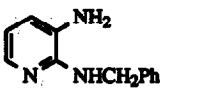
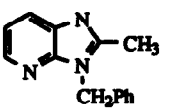
We have extended this study to ethoxymethylenemalononitrile (**6**) and find that in many cases it may be the reagent of choice. This is likely due to the lower pKa of malononitrile (11.2) relative to diethyl malonate (13.3).[7] The pKa difference renders the malononitrile a better leaving group, and in many cases, it can also facilitate the workup since the by-product malononitrile is easily extracted away from the product with aqueous hydroxide.

As illustrated in Table 1, many fused imidazoles were efficiently prepared using the EMM reagents.[8] Yields are generally very good[9] but in some cases, slightly lower yields may reflect a degree of water solubility in the products. Usually, the EMM reagents were interchangeable with no loss of yield, however reactions may require more time with **4**. Additionally, some reactions would only proceed under acidic conditions (entries 4, 5, and 9, Table 1).

Fused imidazoles substituted in the 2 position may also be prepared by using substituted EMM reagents.[10] For example entry 12 shows that 3-benzyl-2-methylimidazolo [4,5-b] pyridine can be readily prepared in high yield from ethoxyethylidenemalononitrile (**7**) and 3-amino-2-benzylaminopyridine.

We attempted to extend this reaction to fused thiazoles and oxazoles and found that the parent benzothiazole

Table 1 Formation of Fused Imidazoles and Related Compounds with EMM Reagents

Entry	Reactant	EMM Reagent	Solvent[a]	Product	% yield[b]
1		4	HOAc		75
2		4	EtOH		87
3		4	Isopropanol		88
4		6	HOAc		89[c]
5		4	Isopropanol		d
6		6	Isopropanol		90
7		6	Isopropanol		79
8		6	Isopropanol		72
9		6	HOAc		67
10		4	HOAc		25[e]
11		6	HOAc		67
12		7	HOAc		88

a. Reactions generally carried out at reflux for 4 to 24 h. b. Yields for isolated purified products. c. Product contained about 5% of an unidentified impurity. d. 65% of intermediate obtained. e. 67% of product is present by NMR of the crude reaction mixture after workup but it is lost during purification by flash chromatography on either silica gel or neutral alumina (activity III). However, the purified product was stable when stirred with silica gel in methanol solution.

was easily prepared. In contrast, 2-aminophenol was very sluggish in reacting with the EMM reagents **4** or **6** and produced several unidentified products and little benzoxazole. However, 3-amino-2-naphthol reacted with **7** to produce the desired oxazole product (67% based on NMR) but the product proved to be difficult to isolate

efficiently from the reaction mixture (entry 10). Thus this method is not useful for the synthesis of fused oxazoles.

The examples described herein serve to highlight a useful and efficient method to prepare fused imidazoles which appears to also have application to fused thiazole synthesis. The ease of reaction, neutral reaction conditions, and simplicity of product isolation make this procedure the method of choice for transformations of this type. The overall process nicely demonstrates that EMM reagents can function as synthons to deliver carbon in the acid oxidation state to ortho diamines and related species.

References and Notes

1 Phillips, M.A. *J. Chem. Soc.*, 1928, 2393-2399. Dubey, P.K.; Ratnam, C.V. *Indian J. Chem.*, 1978, *16B*, 531-533.

2 Stanovnik, B.; Tisler, M. *Synthesis*, 1974, 120-122.

3 See for example Mantlo, N.B.; Chakravarty, P.K.; Ondeyka, D.L.; Siegl, P.K.S.; Chang, R.S.; Lotti, V.J.; Faust, K.A.; Chen, T.-B.; Schorn, T.W.; Sweet, C.S.; Emmert, S.E.; Patchett, A.A.; Greenlee, W.J. *J. Med. Chem.*, 1991, *34*, 2919-2922. Thomas, A.P.; Allot, C.P.; Gibson, K.H.; Major, J.S.; Masek, B.B.; Oldham, A.A.; Ratcliffe, A.H.; Roberts, D.A.; Russell, S.T.; Thomason, D.A. *J. Med. Chem.* 1992, *35*, 877-885. See also U.S. Patent 5,128,325 to Merck and Co. U.S. Patent 5,132,216 to Merck and Co. German Patent DE 4,031,601 to Dr. Karl Thomae GmbH.

4 See for example: Quinn, R. J.; Scammells, P. J.; Kennard, C. H. L.; Smith, G. *Aust. J. Chem.*, 1991, *44*, 1795-1801. Konakahara, T.; Sugama, N.; Sato, K. *Heterocycles*, 1992, *33*, 157-160. Reidlinger, G. H.; Junek, H. *Synthesis*, 1991, 835-8. Schmidt, H. W.; Junek, H. *Liebigs Ann. Chem.*, 1983, 695-704.

5 Nagahara, K.; Kaname, T.; Ueda, T. *Chem. Pharm. Bull.*, 1976, *24*, 1310-1313.

6 For another example of the use of diethyl ethoxymethylenemalonate as a formic acid equivalent in a two step ring forming reaction for β-carboline synthesis see: Calloway, J. C.; Morimoto, H.; Gynther, J.; Airaksinen, M. M.; Williams, P. G. *J. Label. Compound. Radiopharm.*, 1992, *31*, 355-364.

7 Malononitrile pKa: Pearson, R. G.; Dillon, R. L. *J. Amer. Chem. Soc.*, 1953, *75*, 2439. Diethyl malonate pKa: Pearson, R. G.; Mills, J. M. *J. Amer. Chem. Soc.*, 1950, *72*, 1692.

8 All new products were characterized by 250 MHz NMR and gave acceptable elemental analysis and/or high resolution mass spectral analysis.

9 As a typical example entry 8 is described in detail. A mixture of 3-amino-2-cyclohexylamino-pyridine (0.324 g, 1.70 mmol) and ethoxymethylene malononitrile (0.312 g, 2.56 mmol, 1.5 equiv) in isopropanol (10 mL) was refluxed 6 h. The reaction was concentrated and the residue was chromatographed on silica gel (1 x 3 inches). Elution with 2%-20% ethyl acetate - hexane gave 0.02 g of an unidentified impurity. Continued elution with 30% ethyl acetate - hexane gave 0.246 g, 72% of 3-cyclohexyl-imidazolo-[4,5-b]-pyridine as a crystalline solid; NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, J = 1.5, 5 Hz, 1 H), 8.14 (s, 1 H), 8.07 (dd, J = 1.5, 8 Hz, 1 H), 7.24 (dd, J = 5, 8 Hz, 1 H), 4.61 (tt, J = 4, 12 Hz, 1 H), 2.28-2.20 (m, 2 H), 2.05-1.75 (m, 5 H), 1.70-1.47 (sym m, 2 H), 1.45-1.25 (sym m, 1 H). The analytical sample was recrystallized from hexane and had mp 69-70.5°C. Anal. calcd for $C_{12}H_{14}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.47; H, 7.46; N, 20.78.

10 EMM reagents 4, 6, and 7 are all commercially available from Aldrich Chemical Company.

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