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A three-step preparation of MAC reagents from malononitrile

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Abstract—An alternative method for the preparation of MAC reagents, H-C(CN)$_2$O-R, was developed. Using the proposed method, MAC reagents with acyl moiety were synthesized from malononitrile in more than 60% overall yields in three steps.

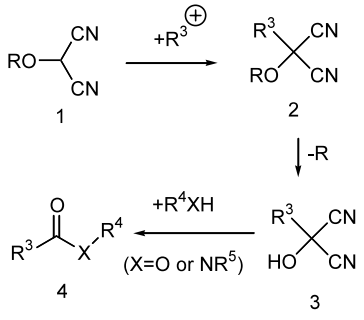
A number of researchers have developed various $^-$COX synthon (X = OH, or the equivalent), which are useful umpolung agents.[1,2] The masked acyl cyanides [**1**, H-MAC-R^3 (MAC = -C(CN)$_2$O-)], a $^-$COX synthon, was developed by us,[4] and then we reported several synthetic applications by using **1** (Scheme 1).[5–8]

All of the transformation reactions from **1** to **4** proceed under mild conditions, and a one-portion reaction can be carried out in some cases.[5,6] However, the availability of **1** has until recently been limited because (i) synthesis from diethyl malonate to **1** requires seven steps and results in less than 10% overall yield (Scheme 2), (ii) conversion from **5** to **6** in ammonia takes up to 10 days when the R group is large, (iii) a basic labile protecting group cannot be introduced as R because one of the seven steps (from **5** to **6**) requires ammonia as a solvent, and (iv) an expensive condensation reagent[9] is required for the final step (from **6** to **1**).

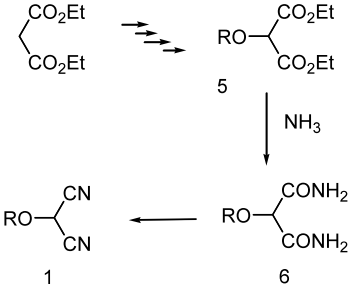
In this paper, we report an alternative method for the preparation of **1** in three steps, and present the synthesis of new MAC reagents **1** with an acyl moiety, one of labile groups under basic conditions. To address the numerous problems outlined above, we examined a synthetic route starting from malononitrile which would eliminate the need for an expensive condensation reagent and ammonia. Direct oxidation of the active methylene of malononitrile was initially attempted using bromine, peroxides, peracids. However, none of these approaches were successful.

Indirect (two-step) activation of the methylene group of malononitrile was then examined via 2-(1-hydroxy-ethylidene)malononitrile **7**, which was prepared according to the standard method[10] in almost quantitative yield from malononitrile (Scheme 3).

Treatment of **7** (208 mg, 1.93 mmol) with 1.2 equiv. of acetic peracid (9% in acetic acid solution, 5 ml, 6.04 mmol) in water (5 ml) for 2 h at room temperature gave



Scheme 1.



Scheme 2.

Keywords: masked acyl cyanide; acyl anion equivalents; alkoxymalononitrile; oxidation; peracids.
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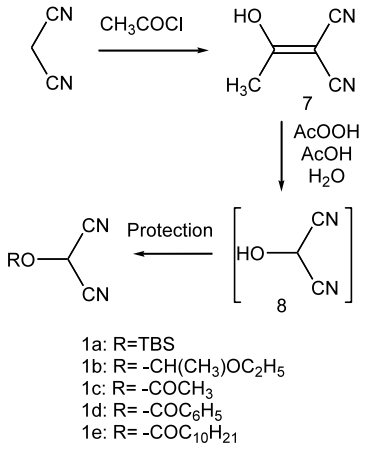

Scheme 3.

the crude product **8**. The resulting solution was concentrated in vacuo to eliminate excess of acetic peracid, water and acetic acid (**Caution***:* during concentration, keep below 35°C in a hood with a hard shield since acetic peracid is explosive). Purification of **8** was unsuccessful because **8** was partially decomposed during silica gel column chromatography. The crude product **8** was then mixed with *t*-butyldimethylsilyl chloride (TBS-Cl, 436.3 mg, 2.90 mmol), and imidazole (197.4 mg, 2.90 mmol) in *N*,*N*-dimethylformamide (5 ml) and stirred for 5 min at 0°C. The resulting mixture was diluted with ethyl acetate, washed with an aqueous solution of sodium hydrogen carbonate/sodium thiosulfate, followed by washing with brine, then dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (8/1) to give H-MAC-TBS (**1a**, 299.3 mg, 1.72 mmol, 79% overall yield from **7**). The ethoxyethyl derivative **1b** (H-MAC-EE) was obtained from the crude **8** using ethyl vinyl ether in the presence of a catalytic amount of 4-toluenesulfonic acid in benzene for 1 h at 0°C in 75% overall yield from **7**. When acetic anhydride was treated to the crude **8** in the presence of pyridine in methylene chloride at 0°C, a new compound **1c** (H-MAC-Ac) was obtained in 63% overall yield from **7**. It is noteworthy that this is the first reported introduction of a basic labile protecting group as R of MAC reagents. Synthesis of the benzoyl derivative **1d** (H-MAC-Bz) and the undecanoyl derivatives **1e**, (H-MAC-$COC_{10}H_{23}$) was also successful, both afforded in 55% overall yield from **7**.

The reaction mechanism for **7** to **8** is proposed as shown in Figure 1. Although reaction course via **9** and **1c** (Baeyer–Villiger type), was initially thought reasonable, that route can be discounted because (i) careful analysis of **7** by ^{1}H and ^{13}C NMR failed to detect the keto form **9**, (ii) not even trace **1c** was obtained as expected for a major Baeyer–Villiger type product, (iii) acidic hydrolysis of **1c** prepared from **8** was not observed at all for more than 24 h under the same reaction conditions as from **7** to **8**. Therefore, the proposed route is considerably via **10** and **11** (epoxidation–ring opening type). After generation of the epoxide **10**, which could be unstable in the presence of large amount of acetic acid, **11** should be produced by ring opening step. Since the product **11** has three electron-withdrawing groups on one carbon, deacetylation would easily occur to give **8**.

In conclusion, a novel method for the synthesis of MAC reagents with very high overall yield has been developed, allowing the various derivatives of MAC reagents to be obtained within several hours using **7**, which is stable and storable for more than 1 month according to the present observation. This advantage will facilitate the development of further synthetic applications using **1**.

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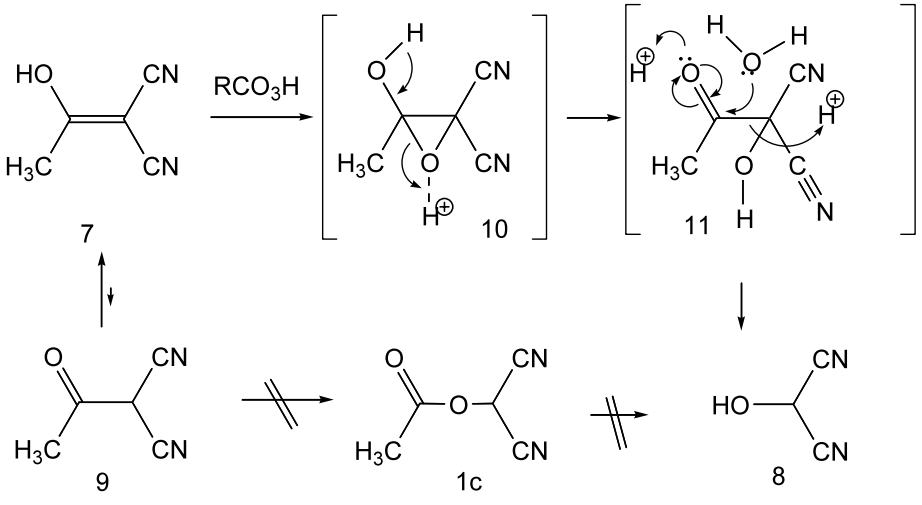

Figure 1.

References

1. Hase, T. A. *Umpoled Synthons*; John Wiley & Sons: New York, 1987 and references cited therein.
2. Nemoto, H. In *Latest Frontiers of Organic Synthesis*; Kobayashi, Y., Ed. Recent advance of organic synthesis by using masked hydroxycarbonyl anions and the related reagents; Research Signport: Kerala India, 2002; pp. 213–226.
3. Abbreviation of MAC: Nemoto, H.; Ibaragi, T.; Bando, M.; Kido, M.; Shibuya, M. *Tetrahedron Lett*. **1999**, 1319–1322.
4. Previous preparation method: Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem*. **1990**, *55*, 4515–4516.
5. Nemoto, H.; Ma, R.; Li, X.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett*. **2001**, *42*, 2145–2147.
6. Nemoto, H.; Ma, R.; Suzuki, I.; Shibuya, M. *Org. Lett*. **2000**, *2*, 4245–4247.
7. Nemoto, H.; Ma, R.; Moriguchi, H.; Suzuki, I.; Shibuya, M. *J. Organomet. Chem*. **2000**, *611*, 445–448.
8. Nemoto, H.; Ma, R.; Ibaragi, T.; Suzuki, I.; Shibuya, M. *Tetrahedron* **2000**, *56*, 1463–1468.
9. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26–31.
10. Hori, I.; Midorikawa, H. Sci. Papers Inst. *Phys. Chem. Res*. **1962**, 216–217.