2-Chloro-1,3-dimethylimidazolinium Chloride. 1. A Powerful Dehydrating Equivalent to DCC

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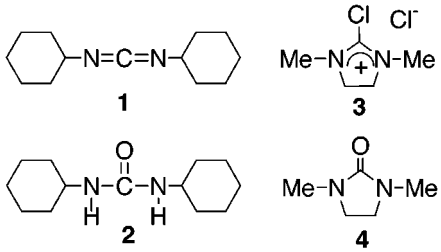
2-Chloro-1,3-dimethylimidazolinium chloride (DMC) (**3**) can act as a powerful dehydrating agent, replacing DCC (**1**) under nearly neutral conditions. Its application to acylation and dehydration is described.

Introduction

Dicyclohexylcarbodiimide (DCC)[1] (**1**) (Chart 1) is widely used in organic reactions as a dehydrating agent because it is inexpensive and can be used under mild conditions. However, it has the disadvantages of low reactivity, and the resulting dicyclohexylurea (**2**) byproduct is relatively insoluble, making the purification of products difficult. Furthermore, it is known that **1** is a potent skin irritant for some individuals.[1a] Although *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI)[2] has also been prepared and is a water-soluble carbodiimide, making the workup procedure more facile, it is expensive.[3]

Chloroamidinium salts such as 2-chloro-1,3-dimethylimidazolinium chloride[4] (DMC)[5] (**3**) and *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium chloride[6] have also been used in dehydration reactions. However, not as much attention has been paid to these reagents until now[7] despite their potential ability to act as dehydrating agents. In our studies on the development of useful reagents for organic synthesis, we focused on **3** as a useful equivalent to **1** because of its low cost[8] and expected nontoxicity.[9] Its synthetic utilities were systematically studied because of its dual advantages of simple preparation from the corresponding cyclic urea, 1,3-dimethyl-2-imidazolidinone (DMI) (**4**) by chlorination, and the easy removal of regenerated **4** after the condensation reaction by washing with water. In this paper we describe in detail the versatility of **3** as an alternative dehydrating agent comparable to **1**.

Chart 1



Results and Discussion

Physicochemical Properties of DMC (3). DMC (**3**), $C_5H_{10}Cl_2N_2$ (169.05), was originally prepared from DMI (**4**) by chlorination with phosgene.[10] However, we prepared **3**[11] by treatment of **4** with trichloromethylchloroformate (diphosgene) or oxalyl chloride in place of phosgene (Scheme 1; see the Supporting Information). DMC (**3**) was obtained as colorless and odorless prisms,

(1) For example, see: (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John-Wiley and Sons: New York, 1967; Vol. 1, pp 231−236. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 349−350.

(2) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John-Wiley and Sons: New York, 1967; Vol. 1, p 274.

(3) The price of EDCI is ¥16500/25 g (Nacalai Tesque, Inc., Japan). This corresponds to $137.5/25 g, based on the exchange rate of ¥120/$ of Japanese yen to U.S. dollars.

(4) Fujisawa, T. Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891.

(5) The CAS No is 37091-73-9. In the *9th Collective Index of Chemical Abstracts* an alternative nomenclature of 2-chloro-4, 5-dihydro-1, 3-dimethyl-1*H*-imidazolium chloride has been adopted. The name of DMC is derived from the chloro derivative of 1, 3-dimethyl-2-imidazolidinone (DMI) (**4**).

(6) Fujisawa, T.; Tajima, K.; Sato, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3529.

(7) Substitution reactions of **3** acting as an electrophile have been reported: Kessler, H.; Kalinowski, H.-O. *Leigibs Ann. Chem.* **1971**, *743*, 1. Kalinowski, H.-O.; Kessler, H.; Walter, A. *Tetrahedron* **1974**, *30*, 1137. Ponti, P. P.; Baldwin, J. C.; Kaska, W. C. *Inorg. Chem.* **1979**, *18*, 873. Isolated examples of the use of **3** as a dehydrating agent can also be found in recent literature. For example, see: Okawa, T.; Eguchi, S. *Tetrahedron Lett.* **1996**, 81. Hirose, M.; Kawai, R.; Hayakawa, Y. *Synlett* **1997**, 495. Iwata, S.; Matsuoka, H.; Tanaka, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1357. Aoyama, T.; Satoh, T.; Yonemoto, M.; Shibata, J.; Nonoshita, K.; Arai, S.; Kawakami, K.; Iwasawa, Y.; Sano, H.; Tanaka, K.; Monden, Y.; Kodera, T.; Arakawa, H.; Suzuki-Takahashi, I.; Kamei, T.; Tomimoto, K. *J. Med. Chem.* **1998**, *41*, 143. Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. *Tetrahedron Lett.* **1998**, *39*, 6331. Okawa, T.; Kawase, M.; Eguchi, S. *Synthesis* **1998**, 1185.

(8) DMC (**3**) is now commercially available in Japan. The price of **3** is ¥9600/25 g (Nacalai Tesque, Inc., Japan). This corresponds to $80/25 g, based on the exchange rate of ¥120/$ of Japanese yen to U.S. dollars. Thus, **3** is about 2-fold cheaper than EDCI.[3]

(9) Although there is no report on the toxicity of DMC (**3**) to our knowledge, the median lethal dose (LD_{50}) of DMI (**4**) in mouse has been reported as 2, 840 mg/kg [Lien, E. J.; Kumler, W. D. *J. Med. Chem.* **1968**, *11*, 214]. This suggests that **3** is basically nontoxic because of easy decomposition of **3** into **4**. On the other hand, cytotoxicity of *N*,*N*,*N*′,*N*′-tetramethylurea, a synthetic precursor for a linear-type chloroamidinium salt, has been reported [Chen, S.; Xu, J. *Tetrahedron Lett.* **1992**, *33*, 647].

(10) Koenig, H.-B.; Wilfried S.; Cologne, H. D.; Metzger, K. G. Ger. Offen. DE 2104579, 1972; *Chem. Abstr.* **1972**, *77*, 140048. Koenig, H.-B.; Schroeck, W.; Disselnkoetter, H.; Metzger, K. G. US 3959258, 1976; *Chem. Abstr.* **1976**, *85*, 160079.

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Scheme 1

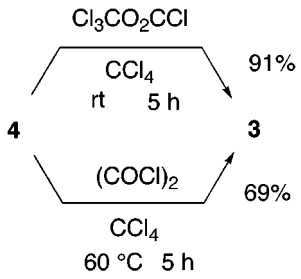


Table 1. Solubilities[a] of 3 in Various Solvents at rt

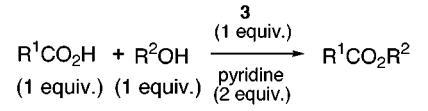
(1) protic solvents[b]		**(3) hydrocarbons**	
AcOH	< 1	n-hexane	> 50
H_2O	< 1	PhH	> 50
MeOH	< 1	PhMe	> 50
EtOH	< 1	**(4) ethers**	
^{i}PrOH	2	Et_2O	> 50
^{n}BuOH	3	$^{i}Pr_2O$	> 50
(2) chlorinated solvents		1,4-dioxane	> 50
		THF	> 50
CH_2Cl_2	< 1	**(5) others**	
$CHCl_3$	< 1	AcOEt	> 50
CCl_4	> 50	MeCOMe	50
$ClCH_2CH_2Cl$	13	MeCN	2
		DMF	6

[a] Solvent/**3** = mL/g. [b] Reactive solvents.

mp 95−100 °C dec. Although **3** is stable to oxygen, it is gradually decomposed in the presence of moisture to produce **4** and hydrochloric acid. Thus, **3** is relatively unstable in protic solvents and the decomposition is accelerated in the presence of a base.[12] However, it is stable at room temperature for over a year when kept desiccated. The solubilities of **3** in various solvents at room temperature are shown in Table 1.

Application of DMC (3) to Organic Synthesis. (I) Acylation. The first reported use[10] of DMC (**3**) as a condensation reagent was in 1972 in the amidation of penicillanic acid. In our studies, we also observed that **3** acted as an effective dehydrating agent in intermolecular condensation reactions between carboxylic acids and a variety of nucleophiles containing an active hydrogen. These reactions occurred under nearly neutral conditions. In a typical experiment, 1 equiv each of a carboxylic acid, a nucleophile, and **3** in a halogenated solvent such as dichloromethane are treated with 2 equiv of an amine (i.e., triethylamine or pyridine) at room temperature, and the crude products are isolated by a standard two-phase partition method (see the Experimental Section). Esters prepared using this procedure are reported in Table 2.[13] A carboxylic acid with an unprotected guanidyl group was esterified smoothly (run 3 in Table 2). Particularly noteworthy was that even a hindered alcohol could be esterified in high yield (run 7 in Table 2). The method was also applicable to the esterification of cycloartenol, a natural triterpene alcohol, with a range of amino acids (Table 3[14]).

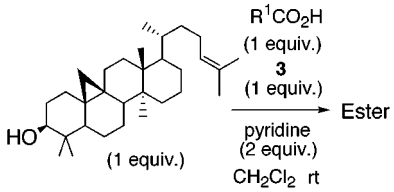
Table 2. Preparation of Esters



runs	R^1	R^2	time (h)	yields[a] (%)
1[13a]	$Me(CH_2)_4$	$PhCH_2$	2	96
2[b]	Ph	Et	2	95
3[13b]	$H_2NC(=NH)NH(CH_2)_5$	4-(EtO_2C)Ph	12	76
4[13c]	^{i}Pr	$Ph(CH_2)_2$	18	93
5[13d]	^{t}Bu	$Ph(CH_2)_2$	20	91
6[13e]	$Ph(CH_2)_2$	^{i}Pr	20	94
7[13e]	$Ph(CH_2)_2$	^{t}Bu	24	88

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

Table 3. Esterification of Cycloartenol



runs	R^1	time (h)	yields[a] (%)
1[14a]	$HCl•Me_2N(CH_2)_3$	72	93
2[14a]	$HCl•Me_2N(CH_2)_2$	12	95
3[14a]	$HCl•Me_2NCH_2$	96	92
4[14b]		68	96

[a] Nonoptimized, isolated yield.

The coupling of other nucleophiles with acids also occurred efficiently. The acylation of 2-mercapto-1,3-thiazoline (Table 4[15]), the preparation of acid anhydrides (Table 5[16]), and the acylation of 1,3-diones (Table 6[17]) were all carried out. In the reaction with diones an

(11) Mukaiyama, T.; Isobe, T.; Kato, M.; Miyagaki, M.; Kogo, S. Jpn. Kokai Tokkyo Koho, JP 59 025375, 1984; *Chem. Abstr.* **1984**, *101*, 151844. Mukaiyama, T.; Isobe, T.; Kato, M.; Miyagaki, M.; Kogo, S. Jpn. Kokai Tokkyo Koho, JP 59 039851, 1984; *Chem. Abstr.* **1984**, *101*, 130410. Kiso and co-workers also reported the preparation of **3** according to our method (Kiso, Y.; Fujiwara, Y.; Kimura, T.; Nishitani, A.; Akaji, K. *Int. J. Peptide Protein Res.* **1992**, *40*, 308).

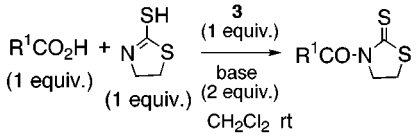
(12) Time-dependent measurement of **3** in CD_3OD using ^{1}H NMR showed 30% and 70% decomposition after 7 and 24 h, respectively, whereas **3** was stable in $CDCl_3$ even after 24 h (6% decomposition). Interestingly, **3** was stable in D_2O (only 3% decomposition after 24 h), but its rapid disappearance was observed in 50% pyridine-d_5 in D_2O (76% and 100% decomposition after 10 min and 3 h, respectively).

(13) References to the products in Table 2 are as follows: (a) Run 1: Korte, W. D. *J. Chromatogr.* **1981**, *214*, 131. (b) Run 3: Muramatsu, M.; Shiraishi, S.; Fujii, S. *Biochim. Biophys. Acta* **1972**, *285*, 224. (c) Run 4: ref 4. (d) Run 5: Ono, N.; Yamada, T.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2401. (e) Runs 6 and 7: Takahashi, S.; Cohen, L. A.; Miller, H. K.; Peake, E. G. *J. Org. Chem.* **1971**, *36*, 1205.

(14) References to the products in Table 3 are as follows; (a) runs 1−3: Isobe, T.; Imai, Y.; Saito, M.; Murata, S.; Nagao, T.; Tsurumi, C. Jpn. Kokai Tokkyo Koho, JP 05 239088, **1993**; *Chem. Abstr.* **1994**, *120*, 134934. (b) Run 4: Kimura, G.; Hirose, Y.; Yoshida, K.; Kuzuya, F.; Fujita, K. Eur. Patent EP 166542, **1986**; *Chem. Abstr.* **1987**, *106*, 18881.

(15) References of the products in Table 4 are as follows. (a) Run 1: Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591. (b) Run 2: Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *53*, 555. (c) Run 3: Isobe, T. Jpn. Kokai Tokkyo Koho, JP 07 010853, 1995; *Chem. Abstr.* **1995**, *123*, 33057. (d) Run 4: Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Chem. Pharm. Bull.* **1984**, *32*, 2687.

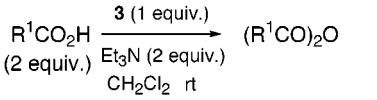
Table 4. Acylation of 2-Mercapto-1,3-thiazoline

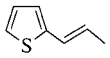
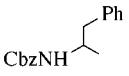


runs	R^1	base[a]	time (h)	yields[b] (%)
1[15a]	^{t}Bu	2,6-L	72	100
2[15b]	Ph	TEA	48	66
3[15c]		2,6-L	48	80
4[15d]	Ph	2,6-L	48	75

[a] 2,6-L = 2,6-lutidine, TEA = triethylamine. [b] Nonoptimized, isolated yield.

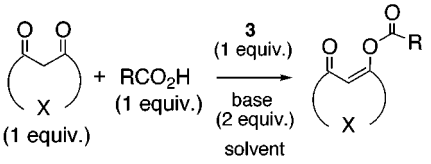
Table 5. Preparation of Acid Anydrides



runs	R^1	time (h)	yields[a] (%)
1[b]	^{t}Bu	4	82
2[16a]	Ph_2CH	25	88
3[16b]		20	90
4[16c]		20	90
5[b]	Me 	18	96
6[16d]	Ph 	23	87
7[16e]		24	94
8[16f]	$Me(CH_2)_7CH{=}CH(CH_2)_7$	43	57

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

Table 6. Acylation of Cyclic 1,3-Diones



runs	R	X	base[a]	sol[b]	temp / time (h)	yield[c] (%)
1[17a]	Et	$(CH_2)_3$	2,6-L	DE	1. rt/17 2. reflux/7	92
2[17b]	Ph	$(CH_2)_3$	TEA	DM	rt/48	91
3[17c]		$(CH_2)_3$	TEA	DM	rt/44	84
4[17a]	Et	O⊤=CH Me	TEA	DE	rt/8	94

[a] 2,6-L = 2,6-lutidine, TEA = triethylamine. [b] sol = solvent; DE = 1,2-dichloroethane, DM = dichloromethane. [c] Nonoptimized, isolated yield.

O-acylation occurred under standard conditions. Interestingly, a C-acylated product[18] was obtained in comparable yield as a single product when the reaction was carried out in the presence of 4-(dimethylamino)pyridine (DMAP) under similar conditions (Scheme 2; see run 1 in Table 6).

Scheme 2

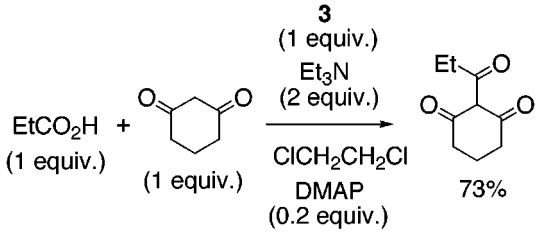
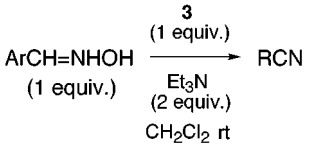


Table 7. Dehydration of Oximes



runs	Ar	time (h)	yields[a] (%)
1[b]	*m*-(NO_2)Ph	24	99
2[b]	3,4,5-$(MeO)_3$Ph	18	99

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

(II) Dehydration. DMC (**3**) proved to be a good dehydrating agent. Thus, aromatic oximes gave nitriles quantitatively (Table 7). This reaction could be effected in one pot from a variety of aldehydes and hydroxylamine hydrochloride (Table 8[19]). Carboxamides were converted into either a nitrile (run 1 in Table 9[20]) or an acylguanidine (run 2 in Table 9), dependent upon the characteristics of the starting materials used. For the formation of the latter product, a carboxamide acted as a nucleophile to **3**. On the other hand, in the presence of trifluoroacetic acid (TFA), nitriles were obtained as sole products (runs 3−5 in Table 9). The product distribution from these reactions appears to be dependent upon the ratio of keto and enol tautomers present, with TFA effectively increasing the relative concentration of the enol form (Scheme 3).

Isocyanides were synthesized from formamides (Table 10[21]). A low yield was observed for the formamide derived from benzylamine (run 4 in Table 10). The poor conversion observed may be caused by the high reactivity of **3**

(16) References to the products in Table 5 are as follows. (a) Run 2: Gerrard, W.; Thrush, A. M. *J. Chem. Soc.* **1953**, 2117. (b) Run 3: ref 6. (c) Run 4: Isobe, T.; Saito, M. Jpn. Kokai Tokkyo Koho, JP 05 025155, 1993; *Chem. Abstr.* **1993**, *119*, 48943. (d) Run 6: Mestres, R.; Palomo, C. *Synthesis* **1981**, 218. (e) Run 7: Miyoshi, M. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3321. (f) Run 8: Patel, K. M.; Morrisett, J. D.; Sparrow, J. T. *J. Lipid Res.* **1979**, *20*, 674.

(17) References to the products in Table 6 are as follows. (a) Runs 1 and 4: Isobe, T. Jpn. Kokai Tokkyo Koho, JP 07 285913, 1995; *Chem. Abstr.* **1996**, *124*, 201688. (b) Run 2: Goldblum, A.; Mechoulam, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1889. (c) Run 3: Anderson, R. J.; Grina, J.; Kuhnen, F.; Lee, S. F.; Luehr, G. W.; Schneider, H.; Seckinger, K. Ger. Offen. DE 3902818, 1989; *Chem. Abstr.* **1990**, *112*, 215765.

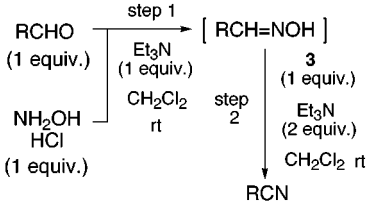
(18) Tabuchi, H.; Hamamoto, T.; Ichihara, A. *Synlett* **1993**, 651.

(19) Reference to the product in run 6 in Table 8 is as follows; Lucier, J. J.; Tuazon, E. C.; Bentley, F. F. *Spectrochim. Acta, Part A* **1968**, *24*, 771; *Chem. Abstr.* **1968**, *69*, 14319.

(20) Reference of the product in run 5 in Table 9 is as follows. Mueller, E.; Kuhner, H. *Chem. Ber.* **1963**, *96*, 670.

(21) Reference to the products in runs 1 and 3 in Table 10 is as follows. Johnson, H. W., Jr.; Krutzsch, H. *J. Org. Chem.* **1967**, *32*, 1939.

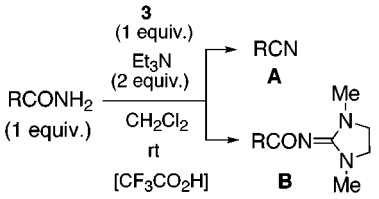
Table 8. Preparation of Nitriles in One-Pot Reaction of Aldehydes and Hydroxylamine Hydrochloride



runs	R	time (h) step 1	time (h) step 2	yields[a] (%)
1[b]		18	42	99
2[b]		17	23	84
3[b]		1	21	80
4[b]	Ph 	4	18	82
5[b]	$Ph(CH_2)_2$	23	46	76
6[19]	$Me(CH_2)_3C(Et)H$	23	49	64

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

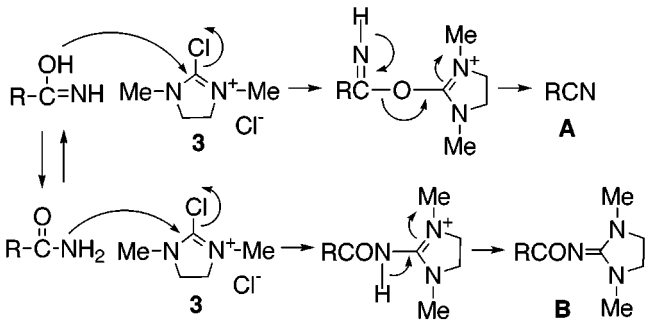
Table 9. Reaction of Carboxamides



runs	R	CF_3CO_2H (1 equiv.)	time (h)	yields[a] (%) A/B
1[b]		-	18	65/0
2	Ph	-	16	0/90
3[b]	Ph	+	4	89/0
4[b]		+	6	84/0
5[20]		+	4	80/0

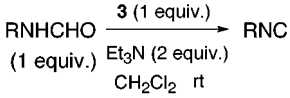
[a] Nonoptimized, isolated yield. [b] The product is commercially available.

Scheme 3



with the benzyl isocyanide product thus formed with **3**. Isothiocyanates (Table 11) and carbodiimides (Table 12[22]) were also prepared from dithiocarbamates and thioureas, respectively. In the latter reactions the use of an aliphatic thiourea resulted in a low conversion to product (run 4 in Table 12).

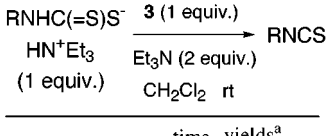
Table 10. Preparation of Isocyanides: Dehydration of Formamides



runs	R	time (h)	yields[a] (%)
1[21]	Ph	72	78
2[b]		48	72
3[21]	4-(MeO)Ph	12	56
4[b]	$PhCH_2$	72	25

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

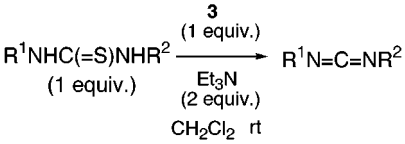
Table 11. Preparation of Isothiocyanates from Dithiocarbamates



runs	R	time (h)	yields[a] (%)
1[b]	Ph	18	92
2[b]		13	92
3[b]	$Ph(CH_2)_2$	17	76

[a] Nonoptimized, isolated yield. [b] The product is commercially available.

Table 12. Preparation of Carbodiimides from Thioureas



runs	R^1	R^2	time (h)	yields[a] (%)
1[22a]	Ph	Ph	4	86
2[22b]	Ph	$Ph(CH_2)_2$	17	88
3[22c]	Ph		21	84
4[22d]	$Ph(CH_2)_2$	$Ph(CH_2)_2$	18	40

[a] Nonoptimized, isolated yield.

Conclusions

The versatility of DMC (**3**) as a dehydrating agent has been clearly demonstrated. It is noteworthy to point out that even nonacidic compounds such as carboxamides or thioureas can be activated by **3**. Thus, DMC (**3**) should

(22) References to the products in Table 12 are as follows. (a) Run 1: Huenig, S.; Lehman, H.; Grimmer, G. *Leibigs Ann. Chem.* **1953**, *579*, 77. (b) Run 2: Fell, J. B.; Coppola, G. M. *Synth. Commun.* **1995**, *25*, 43. (c) Run 3: Petersen, H. J. Ger. Offen. DE 2557438, 1976; *Chem. Abstr.* **1976**, *85*, 142993. (d) Run 4: Anglada, J. M.; Campos, T.; Campos, F.; Moreto, J. M.; Pages, L. I. *J. Heterocycl. Chem.* **1996**, *33*, 1259.

act as a more useful dehydrating agent than DCC (**1**) in organic synthesis because of both its reactivity profile and the ease of product purification. In the following paper in this issue we discuss some additional uses of DMC (**3**) as a dehydrating agent for the construction of heterocycles.

Experimental Section

Commercially available products were directly compared with authentic samples. The physicochemical data of known products were compared with the literature values and those of new products referenced to published values cited in our patents.

General Procedure for Acylation (Tables 2−6). To a solution of a carboxylic acid (1 equiv), a nucleophile (1 equiv), and **3**[23] (1 equiv) in a halogenated solvent was added dropwise an amine (2 equiv) at room temperature. The mixture was stirred at room temperature (in some cases reflux was needed for the completion of the reaction), poured into water, and extracted with dichloromethane. The organic solution was successively washed with 5% HCl, aqueous saturated $NaHCO_3$, and water. It was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by short column chromatography (SiO_2) to give the acylated product.

General Procedure for Dehydration (Tables 7−12). To a solution of a reactant (or reactants) [1 equiv (or each 1 equiv)] and **3**[23] [1 equiv (or 2 equiv)] in an appropriate solvent was added dropwise an amine [2 equiv (or 4 equiv)] at room temperature. The reaction mixture was stirred at room temperature (under reflux in some cases) and then worked up as previously described.

2-Benzoylimino-1,3-dimethylimidazolidine (Run 2 in Table 9). Colorless prisms (from hexane−dichloromethane); mp 85−86 °C. Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.20; H, 7.04; N, 19.44. FABMS *m*/*z* 218 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 6H), 3.60 (s, 4H), 7.36−7.46 (m, 3H), 8.17 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.6, 47.5, 127.7, 129.0, 130.5, 138.3, 164.5, 170.8; IR(KBr) 1560 cm^{-1} (C═O).

Supporting Information Available: The preparation method of DMC (**3**) and selected spectroscopic data for compounds described in our patents. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) DMC (**3**) is essentially stable in dichloromethane.[12] Thus, one can use a pre-prepared solution of **3** in dichloromethane in place of **3** itself as a more convenient method of handling this moisture-sensitive reagent.