Trimethyl Orthoformate as a Highly Selective Mono-C-Methylating Agent for Arylacetonitriles

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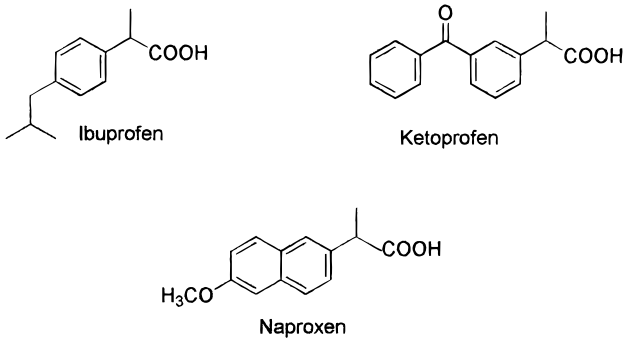
The mono-C-methylation of arylacetonitriles ($ArCH_2CN$, **1**) to produce 2-arylproprionitriles [$ArCH(CH_3)CN$, **2**] represents a valuable reaction especially from a pharmaceutical standpoint. In fact, a number of compounds **2** are key intermediates for the synthesis of nonsteroidal analgesics of the hydratropic acid (2-arylpropanoic acid) class.[1] Common well-known examples are Ibuprofen, Ketoprofen, and Naproxen (Chart 1).

However, synthetic procedures for the direct monomethylation of **1** fail with classical alkylating agents (methyl halides and dimethyl sulfate) because mixtures of mono- and dimethylated products are always obtained (Scheme 1).[2] For instance, the alkylation of phenylacetonitrile with CH_3I is reported with a mono- to dimethyl selectivity of 84%, at a conversion of 86%.[3]

Although a number of multistep alkylation methods have been developed for the preparation of 2-arylpropanoic acids,[1] the achievement of an effective one-pot procedure still represents a challenging task and may deserve attention from both the economical standpoint and the synthetic feasibility.

Concerning this, a very efficient procedure is the ruthenium-catalyzed reductive methylation of active methylene compounds carried out at 135−230 °C with paraformaldehyde.[4] However, we extensively reported that direct highly selective mono-C-methylations of CH_2-acidic compounds (YCH_2X) can also be performed by the use of dimethyl carbonate (DMC) as a methylating agent, without any metal catalyst.[5−11] Thus, at 180−210 °C in the presence of weak bases (K_2CO_3), aryl- and aroxyacetonitriles, methyl aryl- and aroxyacetates (Y = Ar, ArO; X = CN, CO_2CH_3), and α-methylene sulfones (Y = Ar, X = SO_2Ar, SO_2R) yield the corresponding mono-C-methyl derivatives with selectivities >99% at a complete substrate conversion. In addition, the procedure is a true environmentally benign one: DMC is a nontoxic reagent,

Chart 1. Nonsteroidal Analgesics



Scheme 1

X = Cl, Br, I, OSO_3CH_3

the base can be used catalytically, and neither organic nor inorganic byproducts are formed and need to be disposed of.[12,13]

In a further effort to conceive new methods for the selective monoalkylation of arylacetic acid derivatives, we explored the applicability of ortho esters as alkylating agents; the attention was focused on trimethyl orthoformate (TMOF). Although ortho esters are most commonly used for the preparation of ketals and acetals through transacetalation, transetherification, and reduction reactions,[14a,15−18] some successful TMOF-mediated N-methylations of aromatic amines and imidazole-like compounds have also been claimed.[19−21] More generally, ortho esters have been reported as highly selective O-alkylating agents of primary alcohols in the presence of a montmorillonite catalyst.[22] Some years ago, we also reported that, at 195 °C and under basic conditions, TMOF could react with phenol, thiophenol, and phenylacetonitrile to yield the corresponding O-, S-, and C-methylated derivatives;[23] however, while anisole and thioanisole were obtained by using K_2CO_3 as a base, the reaction of phenylacetonitrile proceeded only with *t*-BuOK and we noticed that a selective mono-C-methylation was elusive.

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Table 1. Reaction of Phenylacetonitrile with Trimethyl Orthoformate Carried Out in the Presence of *t*-BuOK and Different Cosolvents[a]

					products (%)[d]			
entry	*T* (°C)	cosolvent, (A/C_s)[b]	time (min)	convn,[c] (%)	**2a**	**3a**	**4a**	others
1	190		60	96	28	11	25	32
2	140		90	85	19	4		60
3	190	DMF (4)	180	72	36	5		31
4	190	MeOH (4)	200	98	70	trace (<1)	28	
5	160	MeOH (4)	180	42	4		38	

[a] All reactions were carried out in an autoclave loaded with a mixture of $PhCH_2CN$ (0.5 g, 4.3 mmol), TMOF (20 mL), and *t*-BuOK (0.96 g, 8.6 mmol) in a 1:43:2 molar ratio, respectively. [b] A/C_s is the volumetric ratio (mL/mL) between TMOF (A) as the alkylating agent and the cosolvent (C_s) (entries 3−5). [c] % determined by GC. [d] **2a**, 2-phenylpropionitrile [$PhCH(CH_3)CN$]; **3a**, 2-phenylisobutyronitrile [$PhC(CH_3)_2CN$]; **4a**, phenylacetic acid ($PhCH_2COOH$); others, unidentified high-boiling products. % determined by GC.

We wish to report here that, in the presence of *t*-BuOK, TMOF may allow a one-pot transformation of arylacetonitriles into the corresponding 2-aryl proprionitriles with excellent monomethyl selectivities (up to 98−99% at conversions of 96−98%) providing that reactions be performed in the presence of suitable amounts of methanol as a cosolvent.

Results and Discussion

A first set of experiments was planned by using phenylacetonitrile (**1a**) as a model compound. As before mentioned, under basic conditions, a high temperature (≥190 °C) was necessary for TMOF to act as a C-methylating agent, plausibly through a $B_{Al}2$ mechanism.[14b] Thus, all the reactions were carried out at 190−210 °C by loading an autoclave with a mixture of **1a** (0.5 g; 4.3 mmol), TMOF (20 mL), and *t*-BuOK (amount: see Table 1). Experiments were performed in the presence of different cosolvents in order to explore whether the medium polarity could have an effect in tuning the selectivity toward the monomethylated product: to this aim, DMF and MeOH were used.[7] Each was added separately to the mixture of the reagents in different volumetric ratios with respect to TMOF (see Table 1). This latter reagent was used in a large excess acting both as the methylating agent and the solvent. Table 1 reports the results.

Experiments 1−4 refer to the use of the base in a 2 molar excess with respect to the substrate. When no cosolvents are used, the reaction of **1a** with TMOF is rapid though nonselective: at nearly quantitative conversions (85−96%), mixtures of mono- and dimethylated products [$PhCH(CH_3)CN$ (**2a**) and $PhC(CH_3)_2CN$ (**3a**)] are always observed along with $PhCH_2COOH$ (**4a**) and other unidentified high-boiling compounds (entries 1 and 2).[24]

Instead, the use of cosolvents dramatically influences the reaction outcome. At 190 °C, in the presence of DMF (TMOF/DMF = 4 volume ratio), although the reaction becomes slower (72% conversion after 180 min), the extent of monomethylated products increases: **2a** and **3a** are observed in a 36 and 5% amounts, respectively, while the sum of other products is 31% (entry 3). A further and marked improvement of the selectivity toward the monomethyl derivative **2a** is achieved by the addition of MeOH as a cosolvent. Under the same conditions used for DMF (190 °C; TMOF/MeOH = 4 volume ratio), the presence of MeOH allows the methylation of **1a** to proceed quantitatively (98% conversion after 200 min) yielding **2a** in a 70% amount, only traces of **3a** (<1%), and **4a** as the sole detectable byproduct (25%) (entry 3 and Scheme 2). At a lower temperature (160 °C), the methylation is markedly slower and $PhCH_2COOH$ becomes the major product (entry 5).

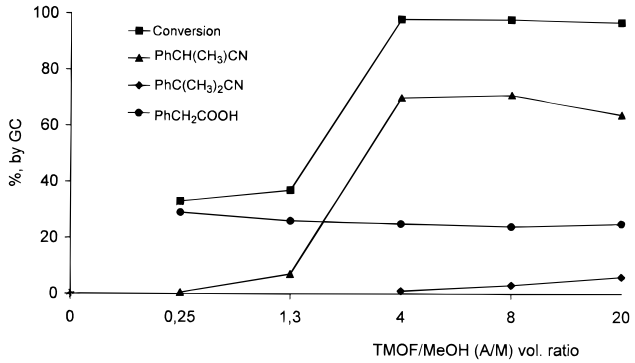

Figure 1. TMOF-mediated methylation of phenylacetonitrile carried out at 190 °C and in the presence of different amounts of MeOH as a cosolvent.

Scheme 2

$$PhCH_2CN \xrightarrow[MeOH]{190\ ^\circ C,\ TMOF} \underset{70\%}{PhCH(CH_3)CN} + \underset{<1\%}{PhC(CH_3)_2CN} + \underset{25\%}{PhCH_2COOH}$$

Under the conditions of entry 4, both the rate and the obtainable monomethyl selectivity appear to be rather independent from the TMOF/substrate ratio. In fact, when this is decreased from 43 (the value of Table 1) to 11 (or even to 4.3) by increasing by 4 (or 10) the substrate quantity, no appreciable changes in the reaction time or in the product distribution are observed: after 200 min, conversion is 98 (99) and the **2a**, **3a**, and **4a** amounts are 69 (70), 2 (2), and 25 (25)%, respectively.

Encouraged by the promising monomethyl selectivity observed, we began to investigate whether the TMOF-mediated methylations could be affected by different amounts of both MeOH and *t*-BuOK.

At first, some tests were set up by varying the volume of the added MeOH. Experiments were run at 190 °C by reacting $PhCH_2CN$ in the presence of a 2 molar excess of *t*-BuOK. Figure 1 shows the results for reactions stopped after 180 min. The conversion of the substrate (**1a**) and the related product distributions are reported versus the TMOF/MeOH (A/M) volumetric ratio; two considerations emerge: (i) Under the explored reaction conditions, a very high mono- to di-methyl selectivity

(24) Unless otherwise indicated, the product % indicated in Table 1 as well as those of Tables 2 and 3 represents the % areas of the corresponding gas-chromatographic peaks. However, when authentic samples of compounds **1a**−**4a** were compared to tetradecane as a standard, very similar GC-response factors were observed for them.

Table 2. Monomethylation of Phenylacetonitrile with Trimethyl Orthoformate in the Presence of Different Amounts of Methanol and *t*-BuOK[a]

entry	*T* (°C)	B/S[b] (mol ratio)	A/M[c] (vol ratio)	time (min)	convn[d] (%)	products (%)[e] 2a	3a	4a
1	190	1	4	180	43	41		
				420	55	53	<0.5	
2	210	1	4	465	67	66	0.6	
3	210	1.2	4	435	62	60	0.6	
				840	84	80	1	
4	200	1.5	4	300	96	92	1	1
5	210	1.5	8	570	85	82	2	
6	210	1.2	20	470	91	81	8	
7	190	1.2	8	300	95	88	4	1
8	190	1.2	20	300	93	82	9	2
9	210	0.5	8	950	40	37	<0.5	

[a] All reactions were carried out in an autoclave loaded with $PhCH_2CN$ (0.5 g; 4.2 mmol) and TMOF (20 mL); MeOH as a cosolvent and *t*-BuOK were added as reported in the footnotes *b* and *c*. [b] B/S is the molar ratio between the base (B) and the substrate (S). [c] A/M is the volumetric ratio between TMOF (A) as the alkylating agent and methanol (M) as the cosolvent. [d] % determined by GC. [e] **2a**, **3a**, and **4a** are defined as in Table 1; % determined by GC.

($S_{M/D}$ = 96−99%)[25] is always attained. However, an optimal A/M of 4 may be identified whereby $S_{M/D}$ reaches a maximum of 99%. (ii) Although experiments are performed under a N_2 atmosphere, the formation of $PhCH_2COOH$ appears unavoidable and quite constant throughout all the examined reactions: **4a** is observed in a 25−30% amount regardless of the added methanol.

Under the conditions we found for the highest $S_{M/D}$ (A/M = 4), we then explored whether any base effects could be observable; $PhCH_2CN$ was reacted with TMOF by varying the *t*-BuOK amount over the range of 0.5−1.5 molar equiv with respect to **1a**. Table 2 reports the results.

The decrease of the quantity of *t*-BuOK drastically depresses the reaction rate. At 190 °C and B/S (base/substrate molar ratio) of 1, low conversions (43−55%) are observed even for a prolonged reaction time [compare entry 4 of Table 1 (B/S = 2) to entry 1 of Table 2]. More generally, when B/S ≤ 1.5, a higher reaction temperature becomes necessary to push the methylation at an appreciable rate (entries 2−4). Thus, at a B/S of 1.5, a distinct improvement is observed at 200 °C: after 300 min, the reaction goes to a substantial completion (96% conversion: entry 4).

Despite the higher temperature (210 vs 190 °C) and longer reaction times (300−850 min vs 180 min), all the tested reactions proceed with a very high monomethyl selectivity ($S_{M/D}$ ≥ 99%). In addition, the formation of $PhCH_2COOH$ is observed in only trace amounts (≤2%). A B/S of 1.5 appears to be the best compromise between the monomethylation rate and the byproducts minimization: after 300 min, a conversion of 96% is reached with **2a**, **3a**, and **4a** formed in 92, 1, and 1% amounts, respectively (entry 4).

As far as the formation of **4a** is concerned, this has to be ascribed to a side reaction of hydrolysis of $PhCH_2CN$ taking place concurrently with respect to the methylation process. This behavior is likely to be due to some water (coming from the reagents) whose availability for the hydrolysis is very sensitive to the quantity of *t*-BuOK; in fact, such a reaction becomes important only when the base is in a 2-fold excess with respect to **1a** (B/S = 2, Table 1 and Figure 1).

The data of Figure 1 and of entries 1−4 of Table 2 allow one to get a measure of the importance of both the cosolvent MeOH and the base. While the former (MeOH) deeply influences the methylation selectivity, the latter (*t*-BuOK) mainly affects the reaction rate and the extent of the nitrile hydrolysis. As a further support to this, Table 2 reports the outcomes of the reaction of **1a** with TMOF carried out by using A/M ratios of 8 and of 20 and B/S of 0.5, 1.2, and 1.5 (entries 5−9). These results shows the following: (i) At every given B/S ratio, the decrease of the added methanol produces a drop in the monomethyl selectivity (compare entries 4, 7, and 8) and, concurrently, an increased methylation rate (compare entries 3, 5, and 6); accordingly, the reduction of the cosolvent also allows the methylation to occur at a lower temperature (190 vs 210 °C; compare entries 4 and 8−9). (ii) At every given A/M ratio, the increase of the base amount results in a marked increase of the reaction rate as well, while selectivity is scarcely, if at all, affected (compare entries 3 and 4, 5 and 7, and 6 and 8). Finally, at a S/B ratio of 0.5, the reaction is extremely slow even by using small volumes of MeOH (entry 9).

Sodium methoxide was also used as a base. However, under the conditions of entry 4, Table 2 (200 °C; B/S = 1.5; A/M = 4), the reaction of phenylacetonitrile with TMOF was not as satisfactory as in the case of *t*-BuOK: after 360 min, the conversion was 75% and **2a** and **4a** were observed in 65 and 2% amounts, respectively, the remainder (8%) being unidentified byproducts.

To investigate the synthetic applicability of the explored methylation procedure, both phenylacetonitrile and different arylacetonitriles [Ar: 4-$CH_3OC_6H_4$ (**1b**), 2-$CH_3OC_6H_4$ (**1c**), 4-$CH_3C_6H_4$ (**1d**), 4-ClC_6H_4 (**1e**), and naphthyl (**1f**)] were reacted with TMOF in the presence of MeOH and *t*-BuOK. Table 3 reports the results.

Data for **1a** refer to a reaction carried out under the conditions of entry 4 in Table 2 (A/M = 4, 200 °C, B/S = 1.5) except for the substrate amount which is 10 times larger (5 g instead of 0.5 g); the quantity of the base is also proportionally increased.

As far as the other nitriles are concerned, Table 3 shows that the reaction conditions need to be tuned according to the reactants' structure. Electron-donating substituents of weak and medium strength (4-CH_3−, 4-CH_3O−, and 2-CH_3O−) produce a decrease of the reaction rate with respect to phenylacetonitrile (compare entries 1, 2−3, 7, and 9). The effect is much more evident for **1c** (2$CH_3OC_6H_4CH_2CN$) because also a relevant steric hindrance operates at the ortho position (entries 7 and 8). Therefore, reactions have to be run at 210 °C by increasing the base amount at B/S of 3 (compounds **1b,c**) and of 2 (**1d**). Despite that, no hydrolysis of the substrate to the respective arylacetic acid is observed. However, although no dimethylation occurs, unidentified byproducts form (2−25%; entries 5−10).

The methylation of compounds **1e** (4-$ClC_6H_4CH_2CN$) and **1f** ($C_{10}H_8CH_2CN$) with TMOF may proceed under the same conditions used for **1a** (200 °C, B/S = 1.5, and A/M = 4) with a $S_{M/D}$ of 97% in both cases (entries 12 and 13), though byproducts are observed for **1e** (17−18%; entries 11−12). Some dimethylation (19%) takes place for **1f** only at a very high conversion (96%; entry 14).

(25) Mono- to dimethyl selectivity ($S_{M/D}$) is calculated as: {% of $PhCH(CH_3)CN$/[% of $PhCH(CH_3)CN$ + % of $PhC(CH_3)_2CN$]} × 100, where % is defined in ref 24.

Table 3. Mono-C-Methylation of Different Arylacetonitriles with Trimethyl Orthoformate in the Presence of MeOH and *t*-BuOK[a]

entry	$ArCH_2CN$ (g)	*T* (°C)	B/S[b] (molar ratio)	A/M,[b] (vol ratio)	time (min)	convn[c] (%)	products (%)[d] M	products (%)[d] D	others	yield[e] (%)
1	**1a**, Ar = Ph (5)	200	1.5	4	300	96	93	1		49
2	**1b**, Ar = 4-$CH_3OC_6H_4$ (0.5)	190	1.5	4	300	31	31			
3		200	1.5	4	840	48	48			
4		210	1.8	8	810	50	50			
5		210	2.5	8	570	72	70		2	
6		210	3	8	850	94	87	5	2	37
7	**1c**, Ar = 2-$CH_3OC_6H_4$ (0.5)	210	1.5	4	420	24	19		5	
8		210	3	4	960	72	47		25	
9	**1d**, Ar = 4-$CH_3C_6H_4$ (0.5)	200	1.5	4	360	79	76		3	
10		200	2	4	270	96	82		14	60
11	**1e**, Ar = 4-ClC_6H_4 (0.5)	200	1.5	4	200	78	61		17	
12		200	1.5	4	300	93	73	2	18	39
13	**1f**, Ar = $C_{10}H_8$ (0.5)	200	1.5	4	300	84	82	2		47
14		200	1.5	2.5	380	96	77	19		

[a] All reactions were carried out in an autoclave loaded with the substrate, TMOF (20 mL), and *t*-BuOK in the reported molar ratio. [b] B/S and A/M are the molar and volumetric ratio as defined in footnotes *b* and *c* of Table 2. [c] % determined by GC. [d] % determined by GC; M and D, monomethylated [$ArCH(CH_3)CN$] and dimethylated [$ArC(CH_3)_2CN$] derivatives, respectively; others, unidentified high boiling products. [e] Isolated yields.

These results suggest that the reaction conditions for the methylation of different arylacetonitriles with TMOF need to be optimized case-by-case to avoid (or minimize) the byproduct formation.

The isolated yields of products **2** appear to be moderate (37−60%): these values correspond to the 50−70% of the gas-chromatographic percent of the monomethyl derivatives (**M**) reported in Table 3.[24] Although yields have not been optimized, this result can be also partly ascribed to some decomposition of the starting reagents. This has been observed, for instance, after the distillation of **2a**: a residual tar is recovered as a nondistillable and nonanalyzable (by GC) material.

Conclusions

The here described procedure proposes a new one-pot transformation of arylacetonitriles into 2-arylpropionitriles (**2a**−**f**) by using trimethyl orthoformate as the alkylating agent. The reaction occurs with a high monomethyl selectivity (up to 99%) at complete substrate conversions. Although this preliminary investigation is far from explaining the mechanism responsible for such an intriguing result, it has revealed that the reaction outcome is mostly dependent upon the presence of methanol as a cosolvent. In fact, it is this alcohol that tunes the reaction toward a very selective monomethylation process.

On the other hand, the base used (*t*-BuOK) has major effects on the reaction rate.

Finally, the procedure may also have an environmental significance; in fact, TMOF is by far a less toxic alternative to current methylating agents (e.g. methyl halides or dimethyl sulfate).

Experimental Section

All the compounds used were ACS grade and were employed without further purification. ^1H NMR spectra were recorded at 400 MHz using $CDCl_3$ as the solvent. GC analyses were performed using a 30 m, DB5 capillary column. GC/MS analyses were performed by a mass detector at 70 eV coupled to a gas chromatograph fitted with a 30 m, DB5 capillary column. Melting points are uncorrected.

Reactions Carried Out in Autoclave. General Procedure. All methylation reactions by TMOF were carried out in a stainless steel (AISI 316) autoclave (internal volume of 250 mL), equipped with a purging valve, through which, at room temperature, air was removed before each reaction by purging with N_2 stream. A magnetically stirred mixture of the alkylating agent, the arylacetonitrile, the base (*t*-BuOK), and methanol (where indicated) in the reported molar and volumetric ratios (see Tables 1−3) was heated in the autoclave, itself heated in an electrical oven, at the desired temperature (190−210 °C). The corresponding internal pressure was of 8−12 bar. A thermocouple (T) and a needle valve (V) were fixed onto the autoclave head: while the former (T) (dipping into the reaction mixture) allowed a constant check of the reaction temperature, the latter (V) was connected to a $^1/_8$ in. stainless steel sampling pipe immersed into the reaction mixture. In this way, the internal pressure allowed samples to be withdrawn through V at intervals, during the course of the reaction. Before GC analyses, each sample (0.2−0.3 mL) was cooled to room temperature, added to diethyl ether (2 mL), water (2 mL), and diluted HCl (3 drops), and finally shaken.[26] The organic layer was then analyzed by GC.

Typical Experimental Procedure. Monomethylation of Phenylacetonitrile (Entry 4, Table 2). The above-described autoclave was loaded with a solution of phenylacetonitrile (0.5 g, 4.3 mmol), trimethyl orthoformate (20 mL, 0.18 mol), and methanol (5 mL, 0.12 mol). To this solution, *t*-BuOK (0.72 g, 6.4 mmol) was added. The autoclave was then closed, purged with a N_2 stream, and finally heated in an electrical oven at 200 °C, while the reaction mixture was kept under a magnetic stirring. At intervals (30 min), samples were withdrawn and analyzed by GC: a substantially quantitative conversion of the substrate was observed after 300 min.

Purification of Products. After the reaction was completed, the autoclave was rapidly cooled to room temperature in a water bath. Then, the reaction mixture was transferred into a separatory funnel, added to water (50 mL), and carefully acidified with diluted HCl (10%) until a pH of 4−5 was reached (checked by a pH paper). The organic phase was then extracted with diethyl ether (3 × 50 mL) and the combined layers dried over sodium sulfate and filtered. The light solvents (TMOF and diethyl ether) were removed by rotary evaporation, and the residue was distilled under vacuum (in the case of compound **2a**) or purified by gravity column chromatography for the monomethylated derivatives **2b**,**d**−**f** (silica gel, Merck F60; eluting solvent, diethyl ether/petroleum ether in a 30:70 v/v ratio). The vacuum distillation was performed in a micro-Claisen distillation apparatus with a fused-on Liebig condenser.

(26) The addition of HCl transforms anions such as $ArCH^-CN$, $ArC^-(CH_3)CN$, etc., into the corresponding conjugated acids ($PhCH_2CN$, ...) that can be so analyzed by GC. This hydrolytic workup does not certainly hydrolyze the reacting nitrile **1**. If so, also $ArCH(CH_3)COOH$ (coming from the hydrolysis of **2**) should be observed, but we never detected it.

Compounds **2a**,**b**,**d**,**e** were compared to authentic samples whose full analytical data were previously reported by us;[4] data for **2f** agreed with the reported ones.[27] **2c** was not isolated; its characterization was through GC/MS analysis by comparison to an authentic sample.[4]

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