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Solid-Phase Synthesis of 2,4,6-Trisubstituted Pyridines

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A new solid-phase synthesis of 2,4,6-trisubstituted pyridines from hydroxyacetophenones is described. The synthesis includes Claisen−Schmidt and Michael reactions on Wang resin to produce 1,5-diketones, which are then cyclized with ammonium acetate. The pyridine substituents are introduced independently and are derived from readily available, diverse sets of starting materials. The method is suitable for the synthesis of arrays of compounds.

Introduction

The solid-phase synthesis of heterocyclic ring systems of importance to drug discovery is an active area of research.[1,2] Pyridine derivatives have been used as pharmaceuticals[3,4] and thus are an attractive target for solid-phase synthesis and combinatorial library production. A solid-phase synthesis of 2,3,4,5,6-pentasubstituted dihydropyridines and pyridines has been described by Gordeev.[3] The compounds are prepared by the Hantzsch pyridine synthesis and therefore all contain acyl or carboxyl groups in the 3- and 5-positions (Scheme 1a). The method is particularly well suited for the preparation of dihydropyridines. Another recent report describes a "3 + 3" solid-phase pyridine synthesis from an α,β-unsaturated carbonyl and 3-aminocrotononitrile.[5] All of the pyridines produced by this scheme have a 3-cyano-2-methyl substitution pattern. The chalcone in the latter synthesis is derived from the reaction of 4-carboxybenzaldehyde on Rink resin with a ketone (Scheme 1b). A solution-phase pyridine synthesis analogous to that illustrated in Scheme 1b has also been reported recently.[6] Chalcones are versatile intermediates from which a number of heterocycles can be prepared, so they represent an attractive intermediate when designing a pyridine synthesis.

To prepare a combinatorial library of pyridines with a high degree of potential diversity and wide utility for drug discovery using solid-phase techniques, it is important to design a pyridine synthesis in which at least three components can be independently and readily varied. In the Hantzsch type synthesis (Scheme 1a), the R_1 group is introduced independently, but the R_2 and R_3 groups are introduced in one reagent (aminocrotonate **3**). In the sequence in Scheme 1b, the R group is introduced through an independent step, but the methyl and cyano groups come from one reagent (**7**, generated from acetonitrile). Thus, we looked for an alternate pyridine synthesis in which at least three substituents could be varied independently and for which there was a diverse set of reagents readily available to introduce the variable groups.

The synthesis of pyridines from 1,5-pentanediones and ammonia followed by oxidation is known.[7] This approach appeared promising for a combinatorial pyridine synthesis because the substituents around the pentanedione core could be readily varied. Krohnke has described a variation of this synthesis which involves the reaction of a bromomethyl ketone with pyridine and subsequent reaction of the resultant pyridinium intermediate with an unsaturated ketone in the presence of ammonium acetate in acetic acid to yield a 2,4,6-trisubstituted pyridine.[8] The latter synthesis proceeds through a 1,5-diketone intermediate which is not isolated.

We have recently developed a solid-phase pyridine synthesis that utilizes an α,β-unsaturated carbonyl attached to a solid support but that differs in a number of key aspects from syntheses reported by other workers. The pyridine synthesis described in this paper involves a Claisen−Schmidt reaction to form an α,β-unsaturated carbonyl, a Michael reaction with a trimethylsilyl enol to form a 1,5-pentanedione, and cyclization with ammonium acetate to form a pyridine.

Results and Discussion

As outlined in Scheme 2, a hydroxyacetophenone **9** was attached to Wang chloride resin **10**[9] via the phenolic group with Cs_2CO_3 and NaI in *N*,*N*-dimethylformamide (DMF) to give resin-bound acetophenone **11** in quantitative yield. An ester linkage was not expected to be stable to subsequent reaction conditions, and products with a phenol were of interest because of their potential to interact with steroid receptors. Rink resin was not examined, but an amide linker should be stable under the conditions developed. A Claisen−Schmidt reaction with an aromatic aldehyde (NaOMe/MeOH added dropwise to resin and aldehyde) gave α,β-unsaturated ketone resin **13**. In the case of cyclohexane carboxaldehyde, it was necessary to add a solution of the aldehyde dropwise to a mixture of resin and base. This alternative procedure suppressed self-condensation of the aldehyde. Michael addition of a trimethylsilyl enol **14**, prepared from a methyl ketone according to Drewes,[10] with CsF in dimethyl sulfoxide (DMSO) at 70 °C gave the 1,5-dione **15**. The pyridine ring was formed by reaction of **15** with NH_4OAC in HOAc/DMF for 18 h at 100 °C to give **16**. During heating, the reaction vials were kept open to the atmosphere. Under these reaction conditions, the initially formed dihydropyridine is apparently oxidized. Air oxidation of dihydropyridines has been previously reported.[11] Only the fully aromatic pyridine **17**

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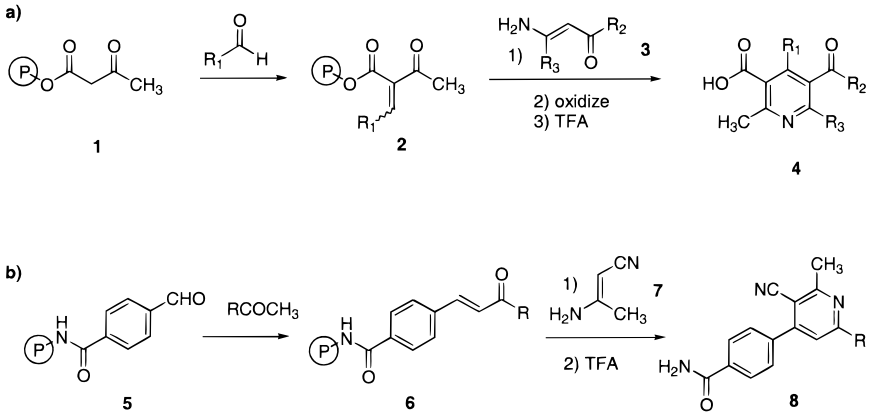
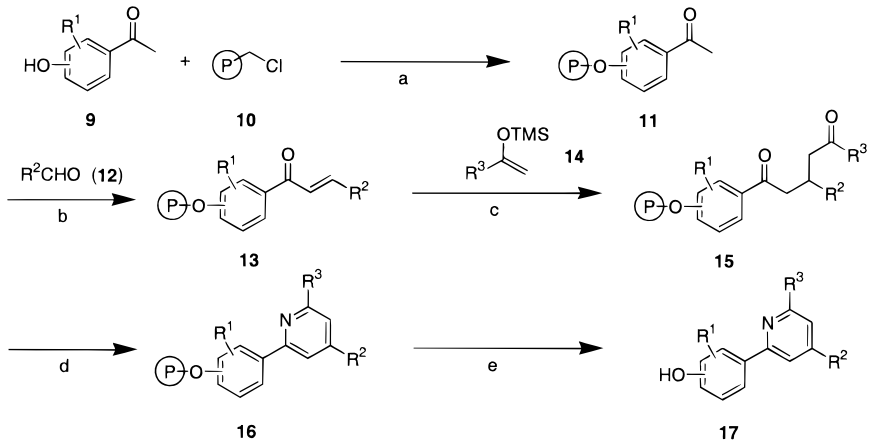
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) Cs_2CO_3, NaI, DMF, 50 °C, 5 h; (b) NaOMe, MeOH, $CH(OMe)_3$, 1−2 h; (c) CsF, DMSO, 70 °C, 3 h; (d) NH_4OAc, HOAc, DMF, 100 °C, 18 h; (e) 50% CF_3CO_2H/CH_2Cl_2, 1 h.

was isolated after cleavage of the product from the resin with 50% CF_3CO_2H/CH_2Cl_2. It is also possible that some or all of the oxidation occurs during the cleavage step.

Representative compounds produced by this synthesis are listed in Table 1. The purities of the crude products, as assessed by HPLC peak area, were generally in the 50−60% range. Compound **17f** was only 21% pure, while **17a** and **17e** had purities of 70% and 81%. In two cases (**17h** and **17j**) side products with peak areas of about 10% were present in the HPLC traces, and there were numerous side products in the HPLC trace of **17f**. None of the side products of **17f**, **17h**, and **17j** have been identified. They do not appear to be either the chalcone or the 1,5-dione intermediates. Overall yields of the products after purification by flash chromatography and crystallization ranged from 19% to 62%.

The R^1−R^3 groups on the pyridine products are derived from readily available reagents. The R^1 substituent is part of the hydroxyacetophenone (**9**), which is the most limited in terms of commercial availability. The R^2 and R^3 groups are introduced via an aldehyde (**12**) and a methyl ketone, respectively. As mentioned above, when the aldehyde R^2 group is cyclohexyl an alternative Claisen−Schmidt procedure is required. The procedure used for preparing the trimethylsilyl enol **14** was only used for cases where the R^3 group is aromatic. Presumably, an alternative procedure would be required for the regioselective preparation of enols from alkyl methyl ketones. Thus, this synthesis is best suited to cases where R^2 and R^3 are aromatic or nonenolizable. There are large and diverse sets of both of these classes of reagents commercially available, so a large number of pyridines are potentially accessible.

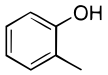
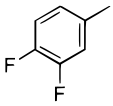
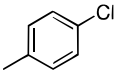
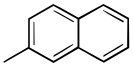
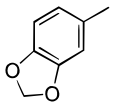
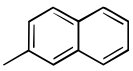
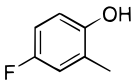
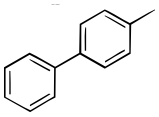
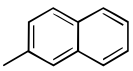
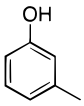
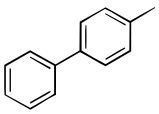
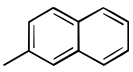
Conclusion

Described in this paper is a new solid-phase synthesis of 2,4,6-trisubstituted pyridines. The synthetic design includes three independently variable groups, R^1−R^3, which are introduced in the scaffold (R^1), from an aldehyde through a Claisen−Schmidt reaction (R^2), and from a methyl ketone through a Michael reaction (R^3). The procedure is quite general and is suitable for the preparation of arrays of compounds.

Experimental Section

2-[6-(4-Chlorophenyl)-4-(3,4-difluorophenyl)pyridin-2-yl]phenol (17a). Step 1: Chloro-Wang Resin (10). A mixture of Wang resin (Advanced ChemTech 200−400 mesh, 1% cross-linked; loading: 0.92 mmol/g; 15.0 g, 0.011 mol), LiCl (1.4 g, 0.033 mol), and DMF (150 mL) was magnetically stirred for 40 min. Collidine (4.0 g, 0.033 mol) was added, and the mixture was cooled (0−5 °C) with an ice bath. Methanesulfonyl chloride (3.8 g, 0.033 mol) was added over 5 min. After 10 min, the cooling bath was removed and stirring was continued for 68 h. The mixture was filtered, and the resin was washed with DMF (250 mL),

Table 1

Compound	Phenol	R^2	R^3	mp, °C	Purity[a]	Yield[b]
17a				146-148	70%	62%
17b	"	"		165-167	57%	46%
17c	"	"		147-148	ND[c]	48%
17d	"			195-196	55%	38%
17e	"	"		120-121	81%	45%
17f				187-188	21%	19%
17g	"	"		oil	56%	51%
17h	"			oil	55%	32%
17i				174-175	50%	34%
17j	"			oil	42%	38%

[a] HPLC peak area. [b] Overall yields for products purified by flash chromatography and/or crystallization. All final products were characterized by ^{1}H NMR, IR, MS, and microanalysis. [c] ND: not determined.

30% H_2O/DMF (2 × 300 mL), DMF (2 × 250 mL), EtOH (3 × 250 mL), CH_2Cl_2 (3 × 300 mL), and hexane (2 × 250 mL). The resin was dried over P_2O_5 in vacuo to give 14.3 g: ^{13}C NMR ($CDCl_3$) δ 46.22 (CH_2Cl); IR (KBr) 2900, 1600, 1520, 1485, 1450 cm^{-1}.

Step 2: 2-Hydroxyacetophenone on Wang Resin (11a). A mixture of **10** (6.0 g, 6.9 mmol), 2-hydroxyacetophenone (**9a**) (34.5 mmol), Cs_2CO_3 (6.7 g, 20.7 mmol), and NaI (1.0 g, 6.9 mmol) in DMF (100 mL) was stirred at 50 °C for 5 h. The resin was filtered and washed with 2:1 DMF/H_2O, 9:1 DMF/H_2O, DMF (×2), and alternating MeOH and CH_2Cl_2 (×4). After drying under high vacuum overnight, 2-hydroxyacetophenone on Wang resin (**11a**) (6.78 g) was obtained.

Step 3: 3-(3,4-Difluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one on Wang Resin (13a). A mixture of (**11a**) (2.0 g, 1.76 mmol) was swelled in trimethyl orthoformate (20 mL) for 10 min. 3,4-Difluorobenzaldehyde (6.0 mmol) was added, and 25% NaOMe in MeOH (0.86 g, 4.0 mmol) was added to the mixture dropwise over 30 min. The mixture was then stirred for an additional 0.5 h. The resin was filtered and washed with alternating MeOH and CH_2Cl_2 (×5) and dried under high vacuum overnight to give 2.17 g of 3-(3,4-difluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one on Wang resin (**13a**). To confirm that the reactions occurred, 2.0 g of resin was treated with 50% TFA/CH_2Cl_2 for 1 h and filtered, and the filtrate was concentrated to give 0.307 g of product. Purification by flash chromatography gave 110 mg (24%) of 3-(3,4-difluorophenyl)-1-(2-hydroxyphenyl)-2-propen-1-one as a yellow solid: mp 138−139 °C; ^{1}H NMR (DMSO-d_6) δ 7.00 (m, 2 H), 7.55 (m, 2 H), 7.75 (m, 1 H), 7.79 (d, J = 15.6 Hz, 1 H), 8.04 (d, J = 15.6 Hz, 1 H), 8.15 (m, 1 H), 8.26 (m, 1 H), 12.44 (s, 1 H); IR (KBr) 1640, 1600 cm^{-1}; MS [M + 1] m/z 261. Anal. Calcd for $C_{15}H_{10}F_2O_2$: C, 69.23; H, 3.87. Found: C, 69.31; H, 3.51.

Step 4: 3-(3,4-Difluorophenyl)-1-(2-hydroxyphenyl)-5-(4-chlorophenyl)-1,5-pentanedione on Wang Resin (15a). 1-Trimethylsilyloxy-1-(4-chlorophenyl)ethylene (1.59 g, 7.0 mmol; prepared according to Drewes[10]) and CsF (0.27 g, 1.76 mmol) were added to a suspension of **13a** (2.0 g, 1.76 mmol) in dimethyl sulfoxide (30 mL). The reaction mixture was heated to 70 °C for 3 h, and the reaction was quenched with 10% AcOH/CH_2Cl_2. The resin was filtered, washed with DMF (×2) and alternating MeOH and CH_2Cl_2 (×5), and dried under high vacuum overnight to give 3-(3,4-

difluorophenyl)-1-(2-hydroxyphenyl)-5-(4-chlorophenyl)-1,5-pentanedione on Wang resin (**15a**).

Step 5: 2-[6-(4-Chlorophenyl)-4-(3,4-difluorophenyl)-pyridin-2-yl]phenol (17a). A mixture of **15a** (2.0 g, 1.76 mmol), NH_4OAc (0.80 g), and AcOH (1.0 mL) in dimethylformamide (20 mL) was heated at 100 °C for 18 h. The resin was filtered, washed with dimethylformamide (×2) and alternating MeOH and CH_2Cl_2 (×5), and dried under high vacuum overnight. The dried resin was treated with 50% TFA/CH_2Cl_2 (15 mL) for 1 h. After filtration of the reaction mixture, the filtrate was concentrated to dryness. The residue was repeatedly dissolved in CH_2Cl_2 (10 mL) and concentrated to remove traces of TFA and purified by flash chromatography to give 2-[6-(4-chlorophenyl)-4-(3,4-difluorophenyl)-pyridin-2-yl]phenol (**17a**): mp 146−148 °C; ^{1}H NMR (DMSO-d_6) δ 6.75 (m, 1 H), 7.00 (m, 2 H), 7.35 (m, 2 H), 7.57 (m, 1 H), 7.69 (d, J = 8.6 Hz, 2 H), 7.95 (d, J = 8.6 Hz, 1 H), 8.18 (d, J = 8.6 Hz, 2 H), 8.32 (m, 2 H), 14.00 (s, 1 H); MS [M + 1] m/z 394. Anal. Calcd for $C_{23}H_{14}ClF_2NO$: C, 70.15; H, 3.58; N, 3.56. Found: C, 69.98; H, 3.51; N, 3.80.

The following compounds, **17b**−**17j**, were prepared according to the procedure described above for **17a**.

2-[4-(3,4-Difluorophenyl)-6-naphthalen-2-yl-pyridin-2-yl]phenol (17b): mp 165−167 °C; ^{1}H NMR (DMSO-d_6) δ 6.99 (m, 2 H), 7.38 (m, 1 H), 7.65 (m, 4 H), 8.06 (m, 4 H), 8.24 (d, J = 6.8 Hz, 1 H), 8.42 (m, 2 H), 8.49 (d, J = 1.2 Hz, 1 H), 8.74 (s, 1 H), 14.35 (s, 1 H); MS [M + H]$^+$ m/z 410. Anal. Calcd for $C_{27}H_{17}F_2NO$: C, 79.21; H, 4.19; N, 3.42. Found: C, 79.33; H, 4.19; N, 3.22.

2-[4-(3,4-Difluorophenyl)-6-furan-2-yl-pyridin-2-yl]phenol (17c): mp 147−148 °C; ^{1}H NMR (DMSO-d_6) δ 6.78 (m, 1 H), 6.98 (m, 2 H), 7.37 (m, 1 H), 7.43 (m, 1 H), 7.67 (m, 1 H), 8.00 (m, 2 H), 8.15 (d, J = 1.3 Hz, 1 H), 8.31 (m, 2 H), 8.39 (d, J = 1.3 Hz, 1 H), 14.26, (s, 1 H); MS [M + H]$^+$ m/z 350. Anal. Calcd for $C_{21}H_{13}F_2NO_2$: C, 72.20; H, 3.75; N, 4.01. Found: C, 71.94; H, 3.62; N, 3.74.

2-(4-Benzo[1,3]dioxol-5-yl-6-naphthalen-2-yl-pyridin-2-yl)phenol (17d): mp 195−196 °C; ^{1}H NMR (DMSO-d_6) δ 6.17 (s, 2 H), 6.99 (m, 2 H), 7.17 (d, J = 8.2 Hz, 1 H), 7.37 (m, 1 H), 7.63 (m, 2 H), 7.71 (dd, J = 8.2, 1.9 Hz, 1 H), 7.83 (d, J = 1.8 Hz, 1 H), 8.03 (m, 1 H), 8.12 (m, 2 H), 8.24 (dd, J = 8.6, 1.8 Hz, 1 H), 8.35 (m, 2 H), 8.42 (d, J = 1.1 Hz, 1 H), 8.74 (s, 1 H), 14.55 (s, 1 H); MS [M + H]$^+$ m/z 418. Anal. Calcd for $C_{28}H_{19}NO_3$: C, 80.56; H, 4.59; N, 3.36. Found: C, 80.13; H, 4.49; N, 3.18.

2-(4-Benzo[1,3]dioxol-5-yl-6-thiophen-3-yl-pyridin-2-yl)phenol (17e): mp 120−121 °C; ^{1}H NMR (DMSO-d_6) δ 6.15 (s, 2 H), 6.97 (m, 2 H), 7.13 (d, J = 8.2 Hz, 1 H), 7.35 (m, 1 H), 7.66 (dd, J = 8.2, 1.9 Hz, 1 H), 7.80 (m, 3 H), 8.16 (d, J = 1.1 Hz, 1 H), 8.31 (m, 2 H), 8.37 (dd, J = 2.9, 1.4 Hz, 1 H), 14.58 (s, 1 H); MS [M + H]$^+$ m/z 374. Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75. Found: C, 70.66; H, 4.02; N, 3.59.

2-(4-Biphenyl-4-yl-6-naphthalen-2-yl-pyridin-2-yl)-4-fluorophenol (17f): mp 187−188 °C; ^{1}H NMR ($CDCl_3$) δ 7.06 (m, 2 H), 7.55 (m, 5 H), 7.69 (m, 3 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.89 (m, 4 H), 8.03 (m, 4 H), 8.12 (dd, J = 8.6, 1.8 Hz, 1 H), 8.47 (d, J = 1.2 Hz, 1 H); MS [M + H]$^+$ m/z 468. Anal. Calcd for $C_{33}H_{22}FNO$: C, 84.78; H, 4.74; N, 3.00. Found: C, 83.98; H, 4.70; N, 2.84.

2-(4-Biphenyl-4-yl-[2,4′]bipyridinyl-6-yl)-4-fluorophenol (17 g): oil; ^{1}H NMR (DMSO-d_6) δ 7.01 (dd, J = 9.0, 5.0 Hz, 1 H), 7.23 (m, 1 H), 7.44 (m, 1 H), 7.53 (m, 2 H), 7.80 (d, J = 7.2 Hz, 2 H), 7.90 (d, J = 8.4 Hz, 2 H), 8.19 (m, 3 H), 8.45 (s, 2 H), 8.53 (s, 1 H), 8.64 (s, 1 H), 9.00 (br s, 2 H); MS [M + H]$^+$ m/z 419. Anal. Calcd for $C_{33}H_{22}FNO\cdot C_2HF_3O_2$: C, 67.67; H, 3.79; N, 5.26. Found: C, 67.42; H, 4.18; N, 5.02.

2-(4-Cyclohexyl-6-furan-2-yl-pyridin-2-yl)-4-fluorophenol (17h): oil; ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 4 H), 1.61 (m, 2 H), 1.76 (m, 4 H), 2.68 (m, 1 H), 6.74 (dd, J = 3.4, 1.8 Hz, 1 H), 6.94 (dd, J = 9.0, 5.1 Hz, 1 H), 7.18 (m, 1 H), 7.26 (d, J = 3.4 Hz, 1 H), 7.72 (s, 1 H), 7.94 (s, 1 H), 8.04 (m, 2 H), 14.22 (s, 1 H); MS [M + H]$^+$ m/z 338. Anal. Calcd for $C_{21}H_{20}FNO_2\cdot 0.2CF_3CO_2H$: C, 71.29; H, 5.61; N, 3.89. Found: C, 71.24; H, 5.74; N, 3.76.

3-(4-Biphenyl-4-yl-6-naphthalen-2-yl-pyridin-2-yl)phenol (17i): mp 174−175 °C; ^{1}H NMR (DMSO-d_6) δ 6.91 (m, 1 H), 7.43 (m, 2 H), 7.60 (m, 4 H), 7.80 (m, 4 H), 7.90 (d, J = 8.4 Hz, 2 H), 8.00 (m, 1 H), 8.12 (m, 2 H), 8.21 (d, J = 8.4 Hz, 2 H), 8.44 (d, J = 1.1 Hz, 1 H), 8.54 (dd, J = 8.6, 1.7 Hz, 1 H), 8.93 (s, 1 H), 9.64 (s, 1 H); MS [M + H]$^+$ m/z 450. Anal. Calcd for $C_{33}H_{23}NO\cdot H_2O$: C, 84.77; H, 5.39; N, 3.00. Found: C, 85.23; H, 5.39; N, 2.83.

3-(4-Cyclohexyl-6-furan-2-yl-pyridin-2-yl)phenol (17j): oil; ^{1}H NMR (DMSO-d_6) δ 1.42 (m, 4 H), 1.71 (m, 2 H), 1.85 (m, 4 H), 2.64 (m, 1 H), 6.67 (dd, J = 3.3, 1.5 Hz, 1 H), 6.85 (dd, J = 8.1, 1.8 Hz, 1 H), 7.18 (d, J = 3.3 Hz, 1 H), 7.29 (m, 1 H), 7.57 (m, 3 H), 7.63 (s, 1 H), 7.85 (s, 1 H), 9.54 (s, 1 H); MS [M + H]$^+$ m/z 320. Anal. Calcd for $C_{21}H_{21}NO_2\cdot 0.6C_4H_8O_2$: C,75.52; H, 6.94; N, 3.77. Found: C, 75.72; H, 6.72; N, 3.55.

References and Notes

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